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(71) Applicant: **ALLERGAN, INC.** [US/US]; 2525 Dupont
Drive, Irvine, CA 92612 (US).

(72) Inventors: **LING, Kah-Hiing, John**; 82 Lessay, Newport
Coast, CA 92657 (US). **YANG, Wu**; 1 Corte Trovata,
Irvine, CA 92606 (US). **NI, Jinsong**; 9 Coca, Foothill
Ranch, CA 92610 (US). **YUAN, Haiqing**; 28 Del Trevi,
Irvine, CA 92606 (US). **TANG-LIU, Diane, D., S.**; 2615
Blackthorn Street, Newport Beach, CA 92660 (US).

(74) Agents: **FISHER, Carlos, A. et al.**; c/o Allergan, Inc.,
2525 Dupont Drive, Irvine, CA 92612 (US).

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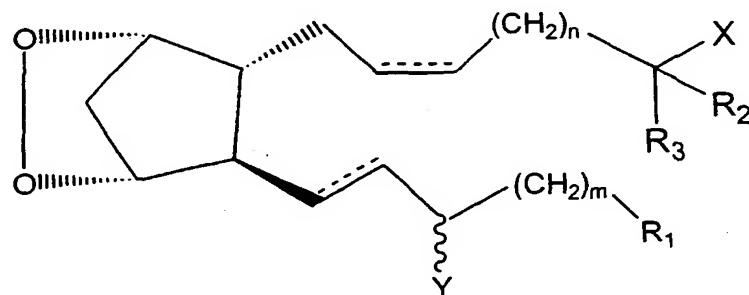
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(54) Title: THE 9, 11-CYCLOENDOPEROXIDE PRO-DRUGS OF PROSTAGLANDIN ANALOGUES FOR TREATMENT OF
OCULAR HYPERTENSION AND GLAUCOMA



(I)

(57) Abstract: 9,11-Cycloendoperoxide derivatives of biologically active prostaglandin analogs, and particularly of the ocular hy-
potensive drugs Bimatoprost, Latanaprost, Unoprostone, Travoprost and prostaglandin H₂ 1-ethanolamide or of structurally closely
related analogs, are pro-drugs which hydrolyze under physiological conditions to provide prostaglandin analogues that are capable
of providing sustained ocular and other in vivo concentrations of the respective drugs. The compounds of the invention have the
formula shown below where the variables have the meaning defined in the specification.

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1 THE 9,11-CYCLOENDOPEROXIDE PRO-DRUGS OF PROSTAGLANDIN
2 ANALOGUES FOR TREATMENT OF OCULAR HYPERTENSION AND
3 GLAUCOMA
4

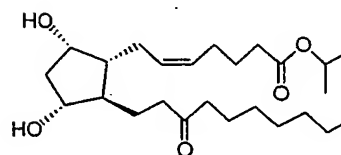
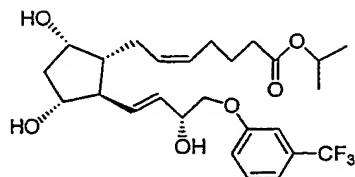
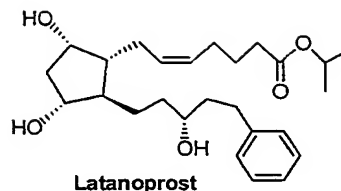
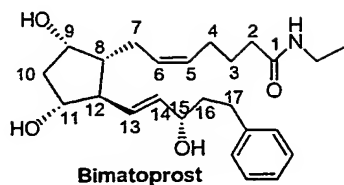
5 BACKGROUND OF THE INVENTION

6 Field of the Invention

7 The present invention is in the field of prostaglandin and analog
8 drugs. More particularly the present invention is in the field of
9 prostaglandin analog drugs which are used for treatment of ocular
10 hypertension, glaucoma or have other useful pharmacological properties.
11 Still more particularly, the present invention is directed to pro-drugs of
12 prostaglandin analogs which are used for treatment of ocular hypertension,
13 glaucoma, have beneficial effects on platelet congregation, gastric
14 ulceration, blood pressure regulation and inflammation.

15 Background Art

16 Several prostaglandin analogs are presently known for their ability to
17 reduce intraocular pressure and can be used for treatment of glaucoma and
18 related diseases of the eye. Among these the drugs known by the names
19 Bimatoprost (U. S. Patent No. 5,688,819) Latanoprost (U. S. Patent Nos.
20 4,599,353, 5,296,504, 5,422,368), Unoprostone (U. S. Patent No.
21 6,329,426) and Travoprost (U. S. Patent Nos. 5,631,287, 5,849,792,
22 5,889,052, 6,011,062) are mentioned as important ones in current use, and
23 are shown by chemical structure below. The conventional numbering of
24 prostaglandins and like structures is indicated in connection with the
25 formula of Bimatoprost.



SUMMARY OF THE INVENTION

In accordance with the present invention 9,11 cycloendoperoxide derivatives of biologically active prostaglandin analogs comprise pro-drugs which hydrolyze under physiological conditions to provide prostaglandin analogues that are capable of providing sustained ocular and other *in vivo* concentrations of biologically active prostaglandin analogues. See *Fredholm et al.*, Prostaglandins 1976, 11, 507-518 and *Stringfellow et al.*, Prostaglandins 1978, 16, 901-910).

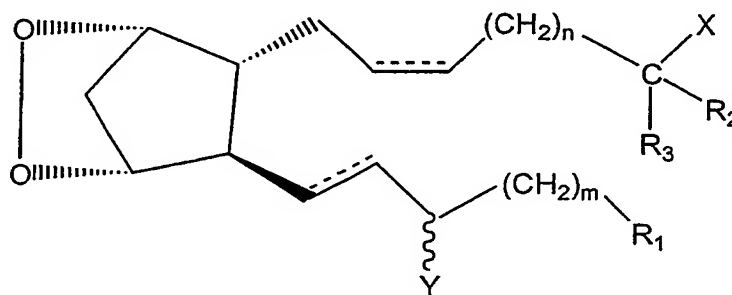
The 9,11-cycloendoperoxide analogs of biologically active prostaglandins are, generally speaking, chemically stable and are converted to the active drugs Bimatoprost, Latanoprost, Unoprostone, Travoprost, and H₂ 1-ethanolamide or to structurally closely related analogs, as well as into other biologically active prostaglandins, such as prostaglandins D₂, E₂, and F_{2α}, thromboxane and prostacyclin analogs, with ocular hypotensive and other biological activity. The thromboxane and prostacyclin analogues effect platelet aggregation and are expected to play a crucial role in preventing gastric ulceration by inhibiting gastric acid secretion, in blood

1 pressure regulation by control of vascular tone, and in inflammation by
2 inhibiting protease secretion of polymorphonuclear leucocytes.

3 In addition to being useful as pro-drugs which hydrolyze under
4 physiologic condition to the corresponding drugs, the 9,11-
5 cycloendoperoxides of the invention may *per se* have the biological activity
6 of the corresponding drug into which they hydrolyze, and as such are
7 expected to provide still better sustained physiological concentration of the
8 therapeutic agent which they represent.

9 The 9,11-cycloendoperoxide pro-drugs of the present invention, in
10 addition to undergoing hydrolysis to provide the corresponding
11 biologically active prostaglandin analogs, also act as substrates to several
12 naturally occurring enzymes which convert the 9,11-cycloendoperoxide
13 pro-drugs into other biologically active analogs wherein the molecular
14 structure is modified. These enzymatic reactions which occur *in vivo* can
15 also be performed *in vitro* by utilizing the corresponding enzymes isolated
16 from human or other mammalian organisms, and are illustrated below in
17 **Reaction Schemes 10 through 20.**

18 The compounds of the invention are generally disclosed by **Formula**
19 **1,**



20 **Formula 1**

21
22 wherein the dashed lines represent the presence of a bond, or absence of a
23 bond, wavy lines represent either alpha or beta configuration, solid triangles

- 1 represent beta configuration and hatched lines represent alpha
2 configuration;
3 **n** is an integer having the values of 1 to 6;
4 **m** is an integer having the values of 1 to 8;
5 **X** is NH_2 , N(R)_2 , NHR , or OR where **R** is hydrogen, R_4 or a $(\text{CO})\text{R}_4$ group;
6 **Y** is $=\text{O}$, $=\text{S}$ or OH , OR_5 or $-\text{O}(\text{CO})\text{R}_5$ groups, said OH , OR_5 or $\text{O}(\text{CO})\text{R}_5$
7 groups being attached to the adjacent carbon in alpha or beta configuration;
8 R_1 is H , CH_3 , R_7 , OR_7 or SR_7 where R_7 is an aliphatic, aromatic or
9 heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms
10 selected from O , S , and N , said aliphatic, aromatic or heteroaromatic ring
11 being optionally substituted with 1 to 3 R_8 groups where R_8 is F , Cl , Br , I ,
12 NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, COOH , or COOR_9 where R_9
13 is alkyl of 1 to 6 carbons or CH_2OCH_3 ;
14 R_2 and R_3 together represent $=\text{O}$, $=\text{S}$, or independently are hydrogen or
15 alkyl of 1 to 6 carbon atoms;
16 R_4 represents $(\text{CH}_2)_r\text{OH}$, $(\text{CH}_2)_r\text{OCOR}_9$ or $(\text{CH}_2)_r\text{OR}_9$ where **r** is an integer
17 having the values 1 to 6, or R_4 represents saturated or unsaturated acyclic
18 hydrocarbons having from 1 to 20 carbon atoms, or $-(\text{CH}_2)_q\text{R}_6$ where **q** is
19 0-10 and R_6 is an aliphatic, aromatic or heteroaromatic ring, said
20 heteroaromatic ring having 1 to 3 heteroatoms selected from O , S , and N ,
21 said aliphatic, aromatic or heteroaromatic ring being optionally substituted
22 with 1 to R_8 groups where R_8 is F , Cl , Br , I , NO_2 , C_{1-6} alkyl, C_{1-6} fluoro
23 substituted alkyl, COOH , COOR_9 where R_9 is alkyl of 1 to 6 carbons or
24 CH_2OCH_3 ;
25 R_5 represents saturated or unsaturated acyclic hydrocarbons having from 1
26 to 20 carbon atoms, or $-(\text{CH}_2)_q\text{R}_6$, or a pharmaceutically acceptable salt of
27 said compound.
28
29

1 DETAILED DESCRIPTION OF THE INVENTION

2 Definitions:

3 As used herein the term alkyl refers to and covers any and all groups
4 which are known as normal alkyl, branched-chain alkyl, cycloalkyl and also
5 cycloalkyl-alkyl. The term alkenyl refers to and covers normal alkenyl,
6 branch-chained alkenyl and cycloalkenyl groups having one or more sites
7 of unsaturation. When referring to saturated or unsaturated acyclic
8 hydrocarbons, the term covers normal alkyl, normal alkenyl and normal
9 alkynyl groups as well as branch-chained alkyl, branch-chained alkenyl and
10 branch-chained alkynyl groups, the normal and branch-chained alkenyl and
11 alkynyl groups having one or more sites of unsaturation.

12 A pharmaceutically acceptable salt may be prepared for any
13 compound in this invention having a functionality capable of forming a salt,
14 for example an acid or amine functionality. A pharmaceutically acceptable
15 salt is any salt which retains the activity of the parent compound and does
16 not impart any deleterious or untoward effect on the subject to which it is
17 administered and in the context in which it is administered.

18 Pharmaceutically acceptable salts may be derived from organic or
19 inorganic bases. The salt may be a mono or polyvalent ion. Of particular
20 interest are the inorganic ions, sodium, potassium, calcium, and
21 magnesium. Organic salts may be made with amines, particularly
22 ammonium salts such as mono-, di- and trialkyl amines or ethanol amines.
23 Salts may also be formed with caffeine, tromethamine and similar
24 molecules. Where there is a nitrogen sufficiently basic as to be capable of
25 forming acid addition salts, such may be formed with any inorganic or
26 organic acids or alkylating agent such as methyl iodide. Preferred salts are
27 those formed with inorganic acids such as hydrochloric acid, sulfuric acid
28 or phosphoric acid. Any of a number of simple organic acids such as
29 mono-, di- or tri- acid may also be used.

1 The compounds of the present invention are capable of existing as
2 *trans* and *cis* (**E** and **Z**) isomers relative to the five-membered ring shown
3 in the respective formulas, and relative to olefinic double bonds. Unless
4 specific orientation of substituents relative to a double bond or the ring is
5 indicated in the name of the respective compound, and/or by specific
6 showing in the structural formula of the orientation of the substituents
7 relative to the double bond or ring, the invention covers *trans* as well as *cis*
8 isomers relative to each center that gives rise to such isomerism, as well as
9 mixtures of *trans* and *cis* isomers.

10 The compounds of the present invention also contain one or more
11 chiral centers and therefore may exist in enantiomeric and diastereomeric
12 forms. Again, unless the name of a compound or its formula specifically
13 describes or shows a specific enantiomer or diastereomer, the scope of the
14 present invention is intended to cover all isomers *per se*, as well as mixtures
15 of *cis* and *trans* isomers, mixtures of diastereomers and racemic mixtures
16 of enantiomers (optical isomers) as well.

17 In the presently preferred compounds of the invention the variable **n**
18 is 3, and the variable **m** is in the range or 1 to 6. The dotted line between
19 carbons 5 and 6 as the numbering is shown on the structure depicting
20 Bimatoprost, preferably represents a bond.

21 The variable **Y** preferably represents =O or OH, or O(CO)**R**₅, where
22 **R**₅ is preferably alkyl of 1 to 6 carbons. Even more preferably **Y** is OH
23 attached to the adjacent carbon with a bond of alpha orientation.

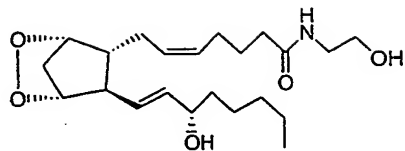
24 In the presently preferred compounds of the invention **R**₁ is methyl,
25 phenyl, phenyl substituted in the phenyl group in the manner described in
26 connection with **Formula 1**, or **R**₁ is O-phenyl, or O-phenyl substituted in
27 the phenyl group in the manner described in connection with **Formula 1**.
28 When **R**₁ is O-phenyl substituted in the phenyl group then the presently
29 most preferred substituent is trifluoromethyl.

1 With respect to the group shown as C(X)(R₂)(R₃) in **Formula 1** the
2 R₂ and R₃ groups preferably jointly form an oxo (=O) function, and the
3 variable X is preferably OH, OR₄ or NHR₄. R₄ is preferably alkyl of 1 to 6
4 carbons, or (CH₂)_rOH where most preferably r is an integer having the
5 value 2.

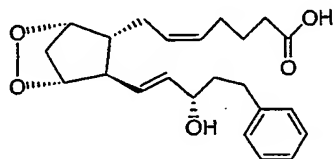
6 The presently most preferred compounds of the invention are the
7 9,11-cycloendoperoxide pro-drugs structurally closely related to
8 Bimatoprost, Latanapost, Unoprostone, Travoprost, Bimatoprost acid and
9 of Prostaglandin H₂ 1-ethanolamide, the chemical structures of which are
10 provided below. Although these structures show specific examples, they
11 nevertheless generally show the 9,11-cycloendoperoxide moiety which can
12 be introduced into the biologically active prostaglandin analogs by the
13 enzymatic synthetic methods described below in detail. Numbers in
14 parentheses next to the 9,11-cycloendoperoxides illustrated below refer to
15 the specific compound numbers which are utilized in the specific
16 description of examples and corresponding reaction schemes.

17 The enzymatic methods utilize the enzyme human COX-2 which
18 can be obtained commercially from Cayman Chemical (Ann Arbor, MI). It
19 was cloned in as described by *Hla et al.* in Proc. Natl. Acad. Sci. USA
20 1992, 89: 7384-7388, incorporated herein by reference. The enzyme was
21 prepared by expression of a DNA clone encoding this enzyme in
22 Baculovirus overexpression system in insect host cells (Sf21 cells).

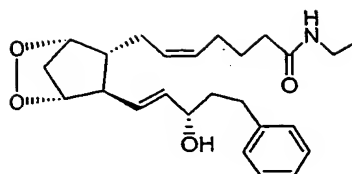
23 The compounds on which the enzymatic syntheses utilizing the
24 enzyme human COX-2 are performed can be prepared by chemical
25 reactions and/or a combination of chemical and enzymatic reactions which
26 are illustrated below, and by such modifications and adaptation of the
27 chemical and/or enzymatic reactions which are within the skill of the
28 practicing synthetic chemist in light of the present disclosure combined
29 with general knowledge and available scientific and patent literature.



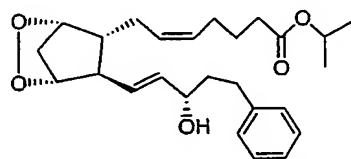
Prostaglandin H₂ 1-ethanolamide (17)



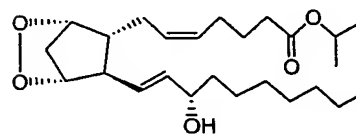
Bimatoprost acid 9,11-cycloendoperoxide (18)



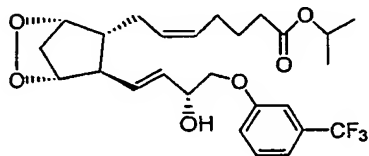
Bimatoprost 9,11-cycloendoperoxide (19)



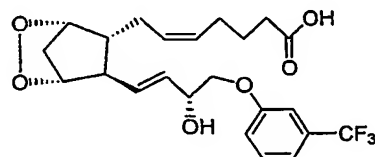
Latanoprost 13,14-dehydro-9,11-cycloendoperoxide (20)



Unoprostone 13,14-dehydro-15-hydroxy-9,11-cycloendoperoxide (21)



Travoprost 9,11-cycloendoperoxide (22)



Travoprost acid 9,11-cycloendoperoxide (23)

1
2

1 BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

2 The compounds of the invention are primarily active as pro-drugs of
3 biologically active prostaglandins or prostaglandin analogs. Because the
4 compounds act primarily as pro-drugs their ultimate biological effect is
5 substantially the same as that of the corresponding drug. However, because
6 the compounds of the invention act as pro-drugs, they tend to release the
7 corresponding drug over a period of time, and therefore are expected to act
8 as a sustained release drug, capable of maintaining a therapeutically
9 effective concentration of the corresponding drug for a longer period of
10 time than the corresponding drug. Still speaking generally, pro-drugs of the
11 present invention are likely to be administered in the same manner as the
12 corresponding drug, and in doses comparable to the administration of the
13 corresponding drug. For specific description of modes of administration
14 and dosages of the known prostaglandin drugs for which the 9,11-
15 cycloendoperoxide compounds of the invention serve as pro-drugs,
16 reference is made to the state of the art and to United States Patent Nos.
17 5,688,819; 5,296,504; 4,599,353; 5,422,368; 6,329,426, 5,631,287,
18 5,849,792, 5,889,052 and 6,011,062 the specification of all which is
19 incorporated herein by reference.

20 The pro-drugs of the present invention may also be administered in
21 combination with the corresponding drug.

22 An important application of several pro-drugs in accordance with the
23 present invention is treatment of ocular hypertension or glaucoma. For this
24 purpose, similarly to the corresponding drug, such as Bimatoprost,
25 Latanaprost, Unoprostone, Travoprost and prostaglandin H₂ 1-
26 ethanolamide, the pro-drug is preferably administered as a topical
27 ophthalmic solution.

28 Still speaking generally, pharmaceutical compositions may be
29 prepared by combining a therapeutically effective amount of at least one

1 compound according to the present invention,* or a pharmaceutically
2 acceptable salt thereof, as an active ingredient, with conventional
3 pharmaceutical excipients, and in some cases by preparation of unit dosage
4 forms suitable for specific use, such as topical ocular use. The
5 therapeutically efficient amount typically is between about 0.0001 and
6 about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid
7 formulations.

8 For ophthalmic application, preferably solutions are prepared using a
9 physiological saline solution as a major vehicle. The pH of such ophthalmic
10 solutions should preferably be maintained between 6.5 and 7.2 with an
11 appropriate buffer system. The formulations may also contain
12 conventional, pharmaceutically acceptable preservatives, stabilizers and
13 surfactants.

14 Preferred preservatives that may be used in the pharmaceutical
15 compositions of the present invention include, but are not limited to,
16 benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate
17 and phenylmercuric nitrate. A preferred surfactant is, for example, Tween
18 80. Likewise, various preferred vehicles may be used in the ophthalmic
19 preparations of the present invention. These vehicles include, but are not
20 limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose,
21 poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified
22 water.

23 Tonicity adjustors may be added as needed or convenient. They
24 include, but are not limited to, salts, particularly sodium chloride,
25 potassium chloride, mannitol and glycerin, or any other suitable
26 ophthalmically acceptable tonicity adjustor.

27 For ophthalmic use various buffers and means for adjusting pH may
28 be used so long as the resulting preparation is ophthalmically acceptable.
29 Accordingly, buffers include acetate buffers, citrate buffers, phosphate

1 buffers and borate buffers. Acids or bases may be used to adjust the pH of
2 these formulations as needed.

3 In a similar vein, an ophthalmically acceptable antioxidant for use in
4 the present invention includes, but is not limited to, sodium metabisulfite,
5 sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated
6 hydroxytoluene.

7 Other excipient components which may be included in the
8 ophthalmic preparations are chelating agents. The preferred chelating agent
9 is edetate disodium, although other chelating agents may also be used in
10 place or in conjunction with it.

11 The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

24 The actual dose of the active compounds of the present invention depends
25 on the specific compound, and on the condition to be treated; the selection
26 of the appropriate dose is well within the knowledge of the skilled artisan.

27 The ophthalmic formulations of the present invention may be
28 conveniently packaged in forms suitable for metered application, such as in
29 containers equipped with a dropper, to facilitate the application to the eye.
30 Containers suitable for drop-wise application are usually made of suitable
31 inert, non-toxic plastic material, and generally contain between about 0.5
32 and about 15 ml solution.

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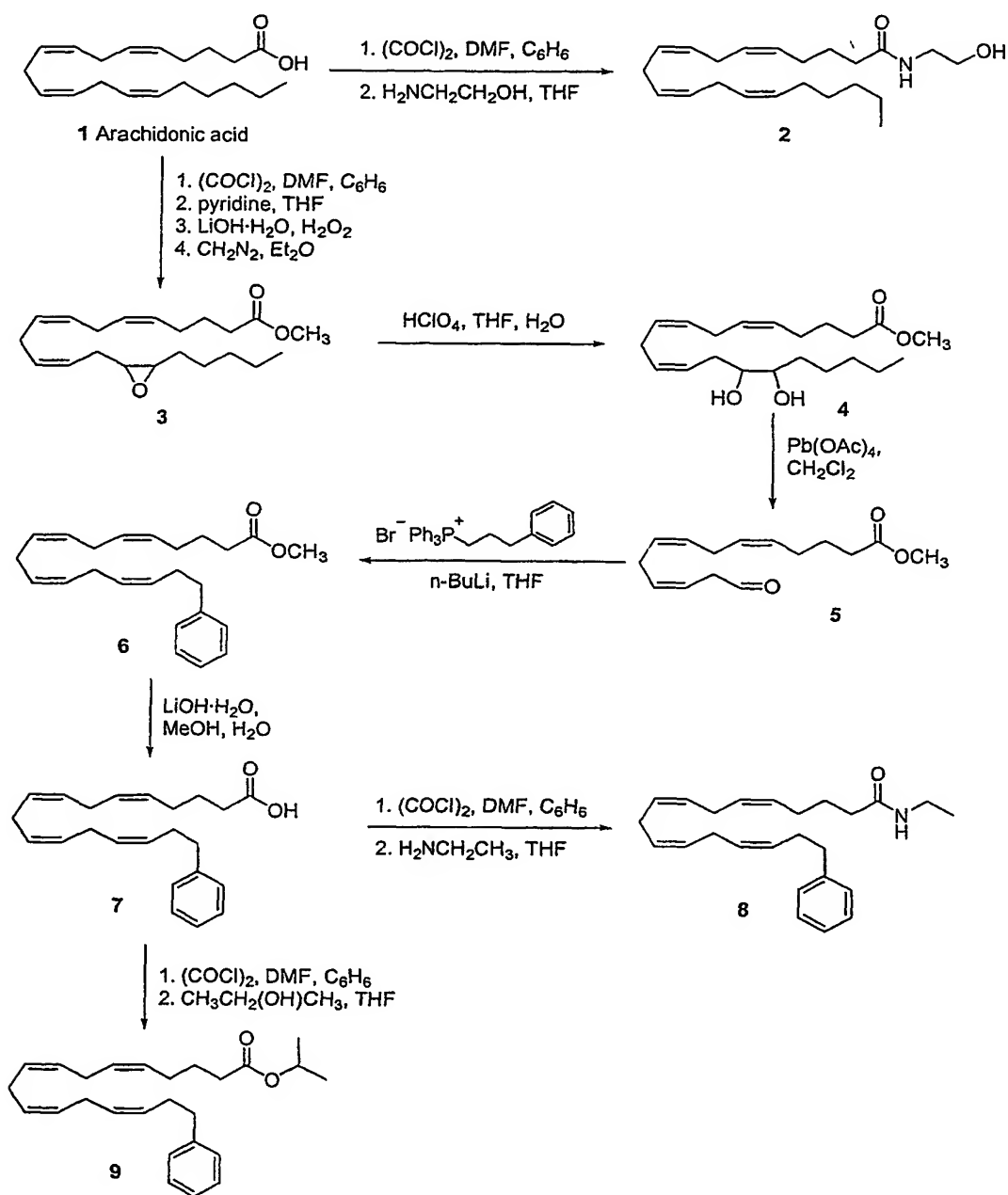
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DESCRIPTION OF SPECIFIC EMBODIMENTS AND
EXAMPLES

General Procedure A

Chemical synthesis of arachidonyl ethanolamide (Compound 2)

The chemical synthesis of arachidonyl ethanolamide from arachidonic acid (**Compound 1**) is illustrated in **Reaction Scheme 1**. Arachidonyl ethanolamide (**Compound 2**) is synthesized following a literature procedure of *Abadji et al.*, J. Med. Chem. 1994, 37, 1889-1893, incorporated herein by reference. To a 0.1 M solution of arachidonic acid (**Compound 1**, available from Cayman Chemical) in anhydrous benzene at 0 °C is added one equivalent of anhydrous dimethyl formamide and two equivalents of oxalyl chloride. The reaction is stirred at room temperature for 1 h and an equal volume of anhydrous tetrahydrofuran (THF) is added. The mixture is then cooled to 0 °C and a 1 M solution of 10 equivalents 2-amino-ethanol in anhydrous THF is added. The reaction is stirred at room temperature until completion. The reaction mixture is then diluted with chloroform, washed successively with 1 M HCl, 1 M NaOH, brine, dried over Na₂SO₄, and concentrated *in vacuo*. The crude product is purified by chromatography on silica gel. Arachidonyl ethanolamide (**Compound 2**) is enzymatically converted into the corresponding 9,11-cycloendoperoxide derivative as shown in **Reaction Scheme 3** and is described below.



REACTION SCHEME 1

1 Chemical synthesis of Compound 3

2 The chemical synthesis of **Compound 3** from arachidonic acid
3 (**Compound 1**) is also illustrated in **Reaction Scheme 1**. **Compound 3** is
4 synthesized by modification of procedures reported by *Ryan et al.* J. Med.
5 Chem. 1997, 40, 3617-3625, based on previous work by *Corey et al.*
6 Tetrahedron Lett. 1983, 24, 37-40 and *Manna et al.* Tetrahedron Lett. 1983,
7 24, 33-36. The *Ryan et al.*, *Corey et al.*, and *Manna et al.*
8 publications are hereby expressly incorporated by reference. To a 0.4 M
9 solution of arachidonic acid (**Compound 1**) in anhydrous benzene at 0 °C
10 are added two equivalents of oxalyl chloride. The mixture is stirred for
11 overnight while allowed to warm to room temperature. The solvent and
12 excess oxalyl chloride is removed *in vacuo*. The resulting crude acid
13 chloride is dissolved in anhydrous THF to make a ~ 2 M solution. Half an
14 equivalent of pyridine is added to the above solution and the mixture is
15 stirred for 10 min at 0 °C. 0.7 M solution of LiOH•H₂O in 50% H₂O₂
16 containing one equivalent of LiOH•H₂O is added and the mixture is stirred
17 for 20 min. The reaction is quenched with pH 7 buffer and brine and
18 extracted with CH₂Cl₂ (×3). The combined organic layer is washed with
19 brine and dried over Na₂SO₄. During this time the epoxy acid is formed
20 and its formation can be monitored by TLC analysis. Upon completion, the
21 drying agent is removed by filtration and the solvent is removed *in vacuo*.
22 The residue is dissolved in anhydrous Et₂O and treated with excess
23 diazomethane. After stirring for 15 min, excess diazomethane is
24 evaporated in a fume hood at room temperature and the solvent is removed
25 *in vacuo*. The crude product is purified by chromatography on silica gel.

27 Chemical synthesis of Compound 4

28 The chemical synthesis of **Compound 4** from **Compound 3** is also
29 illustrated in **Reaction Scheme 1**. **Compound 4** is synthesized following

1 procedures reported by *Ryan et al.* J. Med. Chem. 1997, 40, 3617-3625. A
2 0.05 M solution of **Compound 3** in THF-H₂O (2:1) is treated with five
3 equivalents of 1.2 M HClO₄ at room temperature for overnight. The
4 reaction mixture is then quenched with pH 7 buffer and extracted with
5 EtOAc (×3). The combined organic layer is washed with brine, dried over
6 Na₂SO₄, and concentrated *in vacuo*. The residue is purified by
7 chromatography on silica gel.

8 Chemical synthesis of Compound 5

9 The chemical synthesis of **Compound 5** from **Compound 4** is also
10 illustrated in **Reaction Scheme 1**. **Compound 5** is synthesized following
11 procedures reported by *Ryan et al.* J. Med. Chem. 1997, 40, 3617-3625. A
12 0.2 M solution of **Compound 4** in CH₂Cl₂ at -20 °C is treated with one
13 equivalent of lead (IV) tetraacetate (0.2 M solution in CH₂Cl₂) for 0.5 h.
14 The reaction mixture is filtered through a pad of celite-silica gel and
15 washed with hexane. The solvent is removed *in vacuo* to afford **Compound**
16 **5** which is unstable and is used immediately in the next reaction.

17

18 General Procedure B

19 Chemical synthesis of Compound 6

20 The chemical synthesis of **Compound 6** from **Compound 5** is also
21 illustrated in **Reaction Scheme 1**. **Compound 6** is synthesized by Wittig
22 olefination of **Compound 5** with the ylide triphenyl-(3-phenyl-
23 propylidene)- δ⁵-phosphane. The ylide is generated by adding one
24 equivalent of *n*-butyllithium to a 0.3M solution of triphenyl-(3-phenyl-
25 propyl)phosphonium bromide (available from Lancaster) in THF at -78 °C.
26 After stirring for 30 min, 0.7 equivalent of **Compound 5** in THF is added
27 and the reaction is warmed to room temperature and stirred for 1 h. After
28 completion, the reaction is diluted with hexane, washed successively with

1 pH 7 buffer, brine, dried over Na₂SO₄, and concentrated *in vacuo*. The
2 crude product is purified by chromatography on silica gel.

3

4 General Procedure C

5 Chemical synthesis of Compound 7

6 The chemical synthesis of **Compound 7** from **Compound 6** is also
7 illustrated in **Reaction Scheme 1**. A mixture of **Compound 6** and 7
8 equivalents of lithium hydroxide monohydrate in methanol-water (3:1) is
9 heated to 50 °C until the reaction is complete by TLC analysis. The
10 reaction mixture is cooled to room temperature, quenched with aqueous
11 NH₄Cl and extracted with ethyl acetate (×3). The combined organic layer
12 is washed with H₂O, brine, dried over Na₂SO₄, and concentrated *in vacuo*.
13 The crude product is purified by chromatography on silica gel.

14 **Compound 7** is enzymatically converted into the corresponding 9,11-
15 cycloendoperoxide derivative as shown in **Reaction Scheme 4** and is
16 described below.

17 Chemical synthesis of Compound 8

18 **Compound 8** is synthesized following General Procedure A, using
19 ethyl amine instead of 2-amino-ethanol, as illustrated in **Reaction Scheme**
20 **1**. **Compound 8** is enzymatically converted into the corresponding 9,11-
21 cycloendoperoxide derivative as shown in **Reaction Scheme 5** and is
22 described below.

23 Chemical synthesis of Compound 9

24 **Compound 9** is synthesized following General Procedure A, using
25 isopropyl alcohol instead of 2-amino-ethanol, as illustrated in **Reaction**
26 **Scheme 1**. **Compound 9** is enzymatically converted into the
27 corresponding 9,11-cycloendoperoxide derivative as shown in **Reaction**
28 **Scheme 6** and is described below.

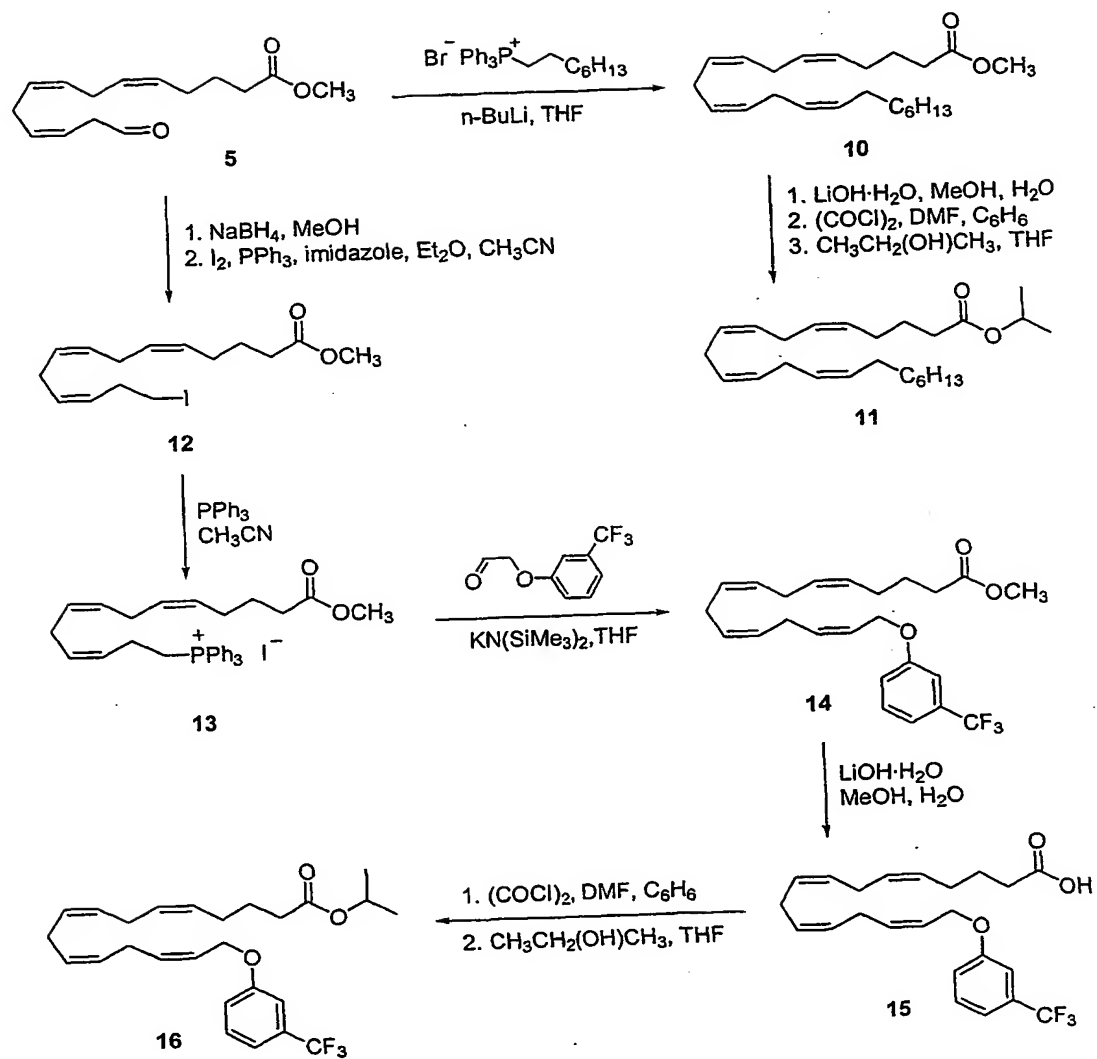
29 Chemical synthesis of Compound 10

1 **Compound 10** is synthesized by Wittig olefination following
2 General Procedure B, using **Compound 5** and (*n*-
3 octyl)triphenylphosphonium bromide (available from Lancaster) instead of
4 triphenyl-(3-phenyl-propyl)phosphonium bromide, as illustrated in
5 **Reaction Scheme 2**.

6 Chemical synthesis of Compound 11

7 **Compound 11** is synthesized in a three step sequence following
8 General Procedure C and General Procedure A, using isopropyl alcohol
9 instead of 2-amino-ethanol as illustrated in **Reaction Scheme 2**.
10 **Compound 11** is enzymatically converted into the corresponding 9,11-
11 cycloendoperoxide derivative as shown in **Reaction Scheme 7** and is
12 described below.

13



REACTION SCHEME 2

1 Chemical synthesis of Compound 12

2 **Compound 12** is synthesized from **Compound 5** following
3 procedures reported by Seltzman (*Seltzman et al.* J. Med. Chem. 1997, 40,
4 3626-3634) and Razdan (*Dasse et al.* Tetrahedron 2000, 56, 9195-9202), as
5 illustrated in **Reaction Scheme 2**. To a 0.25 M solution of **Compound 5** in
6 methanol at 0 °C is added 2 equivalents of NaBH₄. The reaction is warmed
7 to room temperature and is monitored by TLC analysis. After completion,
8 the reaction is quenched with aqueous NH₄Cl and is extracted with EtOAc
9 (×3). The combined organic layer is washed with H₂O, brine, dried over
10 Na₂SO₄, and concentrated *in vacuo*. The crude product alcohol is purified
11 by chromatography on silica gel. This intermediate alcohol is then
12 converted to **Compound 12** following Razdan's procedures (*Dasse et al.*
13 Tetrahedron 2000, 56, 9195-9202.) 1.1 equivalent of I₂ is added portion-
14 wise to a solution of 1.1 equivalent of triphenylphosphine and 1.1
15 equivalent of imidazole in Et₂O-CH₃CN (3:1) at 0 °C. The mixture is
16 stirred at room temperature for 20 min, cooled to 0 °C. To this mixture is
17 added the intermediate alcohol and the reaction is stirred at room
18 temperature for 1 h. The reaction is then diluted with pentane-Et₂O (4:1),
19 filtered through a pad of silica gel to afford **Compound 12**.

20 Chemical synthesis of Compound 13

21 **Compound 13** is synthesized from **Compound 12** following
22 procedures reported by Razdan (*Ryan et al.* J. Med. Chem. 1997, 40, 3617-
23 3625; and *Dasse et al.* Tetrahedron 2000, 56, 9195-9202), as illustrated in
24 **Reaction Scheme 2**. A 0.2 M solution of Compound 12 and 1.1 equivalent
25 of triphenylphosphine in CH₃CN is heated to reflux until completion of the
26 reaction. The solvent is removed *in vacuo* and the residue is purified by
27 washing with hexane-benzene (1:1). The product is dried in a vacuum oven
28 and used directly in the next Wittig reaction.

29

1

2 Chemical synthesis of Compound 14

3 The chemical synthesis of **Compound 14** is illustrated in **Reaction**
4 **Scheme 2**. To a 0.3 M solution of **Compound 13** in THF at -78°C is
5 added 1 equivalent of potassium bis(trimethylsilyl)amide (available from
6 Aldrich). The mixture is stirred at -78°C for 30 min. A solution of 1:5
7 equivalent of (3-trifluoromethyl-phenoxy)-acetaldehyde (prepared by
8 reducing 3-(trifluoromethyl)phenoxyacetonitrile (available from Lancaster)
9 with diisobutylaluminum hydride) in THF is added dropwise to the above
10 mixture and the reaction is gradually warmed to room temperature. Upon
11 completion, the reaction is diluted with heaxans, washed with pH 7 buffer,
12 brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The crude product is
13 purified by chromatography on silica gel.

14 Chemical synthesis of Compound 15

15 **Compound 15** is synthesized from **Compound 14** following
16 General Procedure C as illustrated in **Reaction Scheme 2**. **Compound 15**
17 is enzymatically converted into the corresponding 9,11-cycloendoperoxide
18 derivative as shown in **Reaction Scheme 8** and is described below.

19 Chemical synthesis of Compound 16

20 **Compound 16** is synthesized from **Compound 14** following
21 General Procedure A, using isopropyl alcohol instead of 2-aminoethanol, as
22 illustrated in **Reaction Scheme 2**. **Compound 16** is enzymatically
23 converted into the corresponding 9,11-cycloendoperoxide derivative as
24 shown in **Reaction Scheme 9** and is described below.

25

26 General Procedure D

27 Enzymatic synthesis of 9,11-cycloendoperoxide of Prostaglandin H_2 1-
28 ethanolamide (Compound 17)

1 The human COX-2 catalyzed biosynthesis of Prostaglandin H₂ 1-
2 ethanolamide 9,11-cycloendoperoxide (**Compound 17**) from its
3 arachidonyl ethanolamide (**Compound 2**) is illustrated in **Reaction**
4 **Scheme 3**. The enzyme human COX-2 was obtained commercially from
5 Cayman Chemical (Ann Arbor, MI). It was cloned in 1992 (see the
6 publication by *Hla et al. supra*). The enzyme was prepared by expression
7 of a DNA clone encoding this enzyme in Baculovirus overexpression
8 system in insect host cells (Sf21 cells). Ten μM [³H]arachidonyl
9 ethanolamide (**Compound 2**) with a specific activity of 860 $\mu\text{Ci}/7\text{ mg}$ in 20
10 μl of ethanolic solution was diluted with 960 μl of the COX-2 (hCOX-2)
11 reaction buffer (100 mM Tris-HCl, pH 8.0, containing 2 mM phenol, 5 μM
12 hematin and 1 mM EDTA). One hundred units of hCOX-2 enzyme
13 preparation in 20 μl of hCOX-2 buffer were added to start enzyme reaction.
14 The total incubation volume was 1 ml. The enzyme reaction was stopped
15 by adding 1 ml dry ice-cooled stop solution (ether: methanol: 1 M acetic
16 acid, 30:4:1, v/v) immediately after incubation at 37°C for 2 minutes. The
17 synthesized products were extracted two times with 3 ml of ethyl acetate
18 each. The organic phase was collected and dried at room temperature
19 under nitrogen. The resulting residue was reconstituted in 150 μl of
20 acetonitrile / water (1:1, v/v) for HPLC-Radiometric analysis and
21 LC/MS/MS analysis. The LC/MS/MS analysis of the synthesized 9,11-
22 cycloendoperoxide of prostaglandin H₂ 1-ethanolamide eluting at 31.6
23 minutes indicated that its molecular weight was 395 daltons. The yield of
24 the synthesis as determined by HPLC-Radiometric analysis was 30%.

25 Enzymatic synthesis of Bimatoprost acid 9,11-cycloendoperoxide
26 (**Compound 18**)

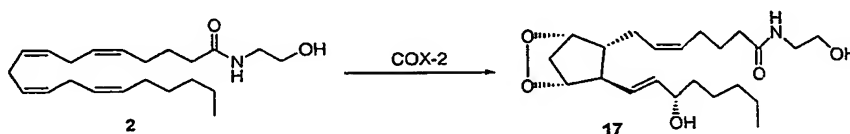
27 Bimatoprost acid 9,11-cycloendoperoxide (**Compound 18**) is
28 synthesized following General Procedure D using **Compound 7**, instead of

1 arachidonyl ethanolamide (**Compound 2**), as illustrated in **Reaction**
2 **Scheme 4**.

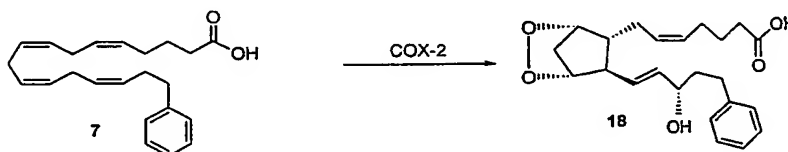
3 Enzymatic synthesis of Bimatoprost 9,11-cycloendoperoxide (**Compound**
4 **19)**

5 Bimatoprost 9,11-cycloendoperoxide (**Compound 19**) is synthesized
6 following General Procedure D using **Compound 8** instead of arachidonyl
7 ethanolamide (**Compound 2**) as illustrated in **Reaction Scheme 5**.

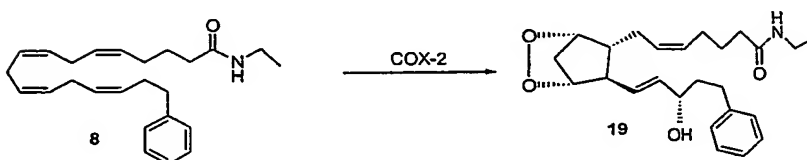
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REACTION SCHEME 3



REACTION SCHEME 4



REACTION SCHEME 5

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12 Enzymatic synthesis of Latanoprost 13,14-dehydro-9,11-cycloendoperoxide
13 **(Compound 20)**

14 Latanoprost 13,14-dehydro-9,11-cycloendoperoxide (**Compound 20**)
15 is synthesized following General Procedure D using **Compound 9** instead

1 of arachidonyl ethanolamide (**Compound 2**), as illustrated in **Reaction**
2 **Scheme 6**.

3 Enzymatic synthesis of Unoprostone 15-hydroxy-9,11-cycloendoperoxide
4 (**Compound 21**)

5 Unoprostone 15-hydroxy-9,11-cycloendoperoxide (**Compound 21**)
6 is synthesized following General Procedure D using **Compound 11** instead
7 of arachidonyl ethanolamide (**Compound 2**) as illustrated in **Reaction**
8 **Scheme 7**.

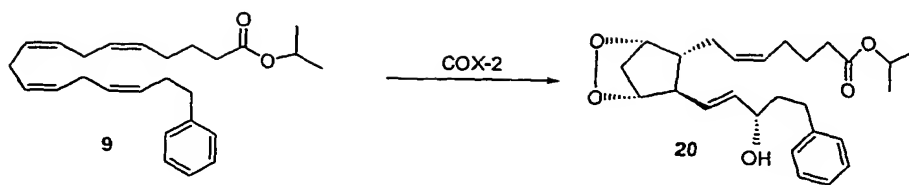
9 Enzymatic synthesis of Travoprost 9,11-cycloendoperoxide (**Compound**
10 **22**)

11 Travoprost 9,11-cycloendoperoxide (**Compound 22**) is synthesized
12 following General Procedure D using **Compound 15** instead of arachidonyl
13 ethanolamide (**Compound 2**) as illustrated in **Reaction Scheme 8**.

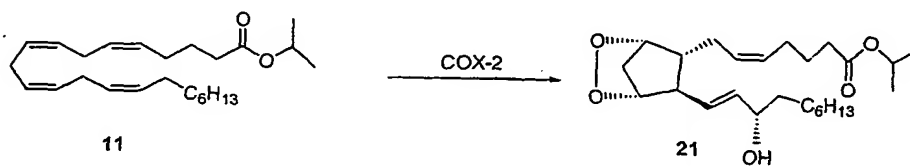
14 Enzymatic synthesis of Travoprost acid 9,11-cycloendoperoxide
15 (**Compound 23**)

16 Travoprost acid 9,11-cycloendoperoxide (**Compound 23**) is
17 synthesized following General Procedure D using **Compound 16** instead of
18 arachidonyl ethanolamide (**Compound 2**) as illustrated in **Reaction**
19 **Scheme 9**.

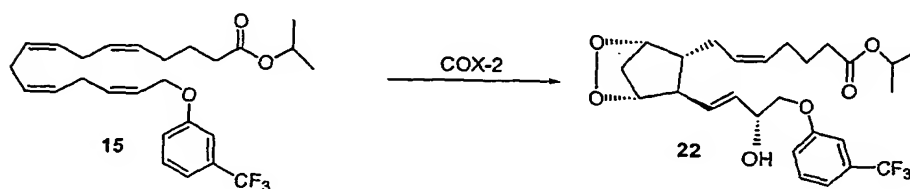
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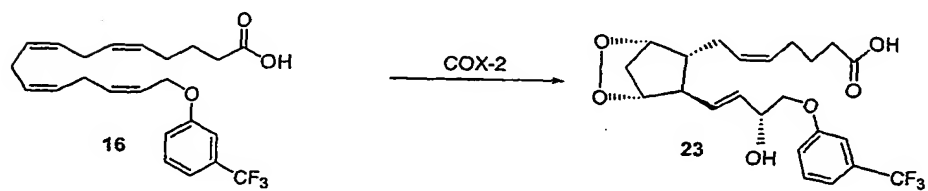
REACTION SCHEME 6



REACTION SCHEME 7



REACTION SCHEME 8

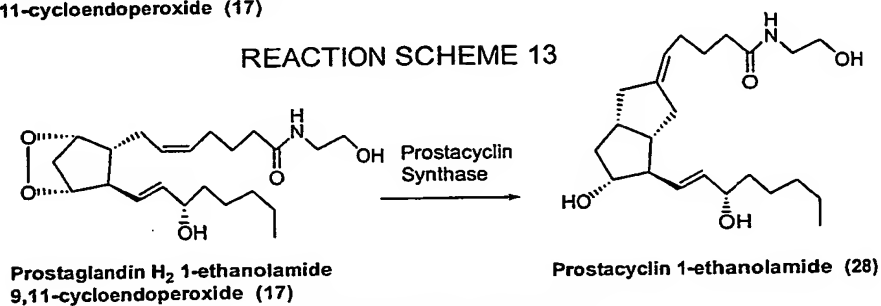
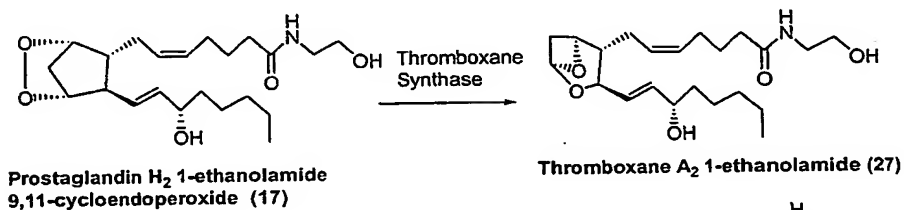
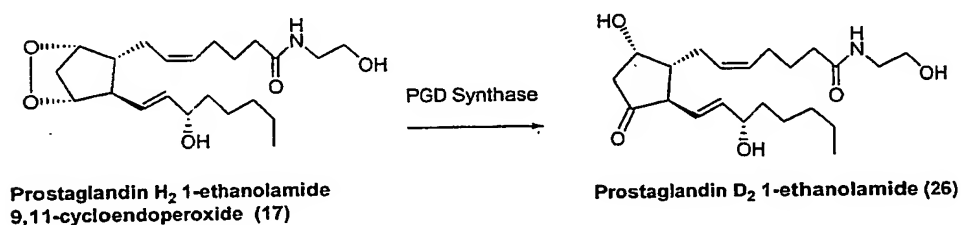
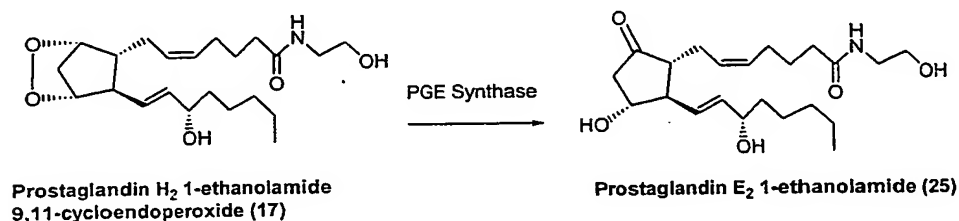
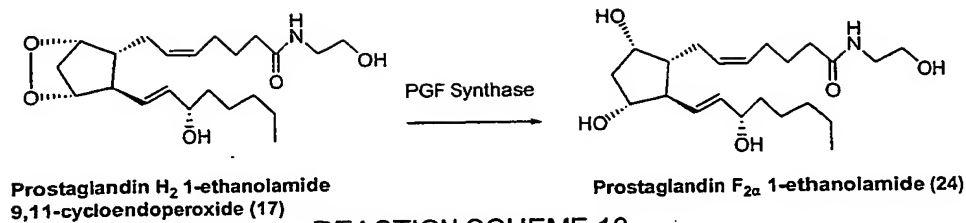


REACTION SCHEME 9

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1 As noted above in the Summary section of the present application for
2 patent, the 9,11-cyclopendoperoxide pro-drugs of the present invention, in
3 addition to undergoing hydrolysis to provide the corresponding biologically
4 active prostaglandin analogs, also act as substrates to several naturally
5 occurring enzymes which convert the 9,11-cyclopendoperoxide pro-drugs
6 into other biologically active analogs. Several of these enzymatic reactions
7 which are expected to occur *in vivo* can be performed *in vitro* in
8 accordance with the present invention resulting in the enzymatic synthesis
9 from the 9,11-cycloendoperoxides of the invention of several biologically
10 active prostaglandin analogs. These enzymatic reactions are illustrated
11 below in **Reaction Schemes 10** through **20**.
12



1
2
3

1 General Procedure E

2 Enzymatic synthesis of Prostaglandin F_{2α} 1-ethanolamide (Compound 24)

3 The human recombinant PGF synthase catalyzed biosynthesis of
4 Prostaglandin F_{2α} 1-ethanolamide from prostaglandin H₂ 1-ethanolamide
5 9,11-cycloendoperoxide (**Compound 17**) is illustrated above in **Reaction**
6 **Scheme 10**. 4.5 μM [³H]Prostaglandin H₂ 1-ethanolamide with a specific
7 activity of 860 mCi/7 mg reconstituted in 0.6 ml of PGF synthase reaction
8 buffer was incubated with 100 μl of the human recombinant PGF synthase
9 solution (1.5 mg/ml) at 37°C for 10 minutes. The cDNA clone of human
10 PGF synthase was isolated from human lung and its enzyme was prepared
11 by expression of cDNA clones in E. coli as described in the publication by
12 *Suzuki-Yamamoto et al.*, FEBS lett, 1999,462: 335-340, incorporated herein
13 by reference. The plasmid was transformed into DH5 α E.coli strain and
14 grown in LB/ampicillin medium. The expressed enzyme in E. coli was
15 partially purified to yield a protein concentration of 15 mg per ml. The
16 pUC8 vectors carrying no PGF synthase DNA insert were also transformed
17 and prepared with protein concentration of 5 mg per ml as a negative
18 control. The enzyme reaction was stopped by adding 1 ml dry ice-cooled
19 stop solution (ether: methanol: 1 M acetic acid, 30:4:1, v/v) immediately
20 after incubation at 37°C for 10 minutes. The synthesized products were
21 extracted with 3 ml of ethyl acetate. The organic phase was collected and
22 dried at room temperature under nitrogen. The resulting residue was
23 reconstituted in 150 μl of acetonitrile / water (1:1, v/v) for HPLC-
24 Radiometric analysis and LC/MS/MS analysis. The prostaglandin H₂ 1-
25 ethanolamide 9,11-cycloendoperoxide was completely converted to
26 prostaglandin F_{2α} 1-ethanolamide in 10 minutes. The product ion spectrum
27 of m/z 398.4 of the biosynthetic product was identical to the standard
28 prostaglandin F_{2α} 1-ethanolamide. They both had the major characteristic
29 fragment ion at m/z 62, which represents protonated 2-amino ethanol

1 group. There was no conversion by the enzyme preparation from same
2 DH5 α cells carrying pUC8 vector without PGF synthase DNA insert. The
3 yield of the synthesis, as determined by HPLC-Radiometric analysis, was
4 94%.

5

6 General Procedure F

7 Enzymatic synthesis of Prostaglandin E₂ 1-ethanolamide (Compound 25)

8 Prostaglandin E₂ 1-ethanolamide is synthesized from prostaglandin
9 H₂ 1-ethanolamide 9,11-cycloendoperoxide (**Compound 17**) following
10 General Procedure E using the human recombinant PGE synthase obtained
11 in accordance with the publication of *Jakobsson et al.* Proc. Natl. Acad.
12 Sci. USA, 1999, 96: 7220-7225, incorporated herein by reference, instead
13 of the human recombinant PGF synthase, as illustrated in **Reaction**
14 **Scheme 11.**

15

16 General Procedure G

17 Enzymatic synthesis of Prostaglandin D₂ 1-ethanolamide (Compound 26)

18 Prostaglandin D₂ 1-ethanolamide is synthesized from its
19 prostaglandin H₂ 1-ethanolamide 9,11-cycloendoperoxide (**Compound 17**)
20 following General Procedure E using the human recombinant PGD
21 synthase obtained in accordance with the publication of *Nagata et al.* Proc.
22 Natl. Acad. Sci. USA, 1991, 88: 4020-4024, incorporated herein by
23 reference, instead of the human recombinant PGF synthase, as illustrated in
24 **Reaction Scheme 12.**

25

26 General Procedure H

27 Enzymatic synthesis of Thromboxane A₂ 1-ethanolamide (Compound 27)

28

1 Thromboxane A₂ 1-ethanolamide is synthesized from prostaglandin
2 H₂ 1-ethanolamide 9,11-cycloendoperoxide (**Compound 17**) following
3 General Procedure E using the human recombinant thromboxane synthase
4 obtained in accordance with the publication of *Miyata et al.*, Eur. J.
5 Biochem, 1994, 224: 273-279, incorporated herein by reference, instead of
6 the human recombinant PGF synthase, as illustrated in **Reaction Scheme**
7 **13**.

8
9 General Procedure I

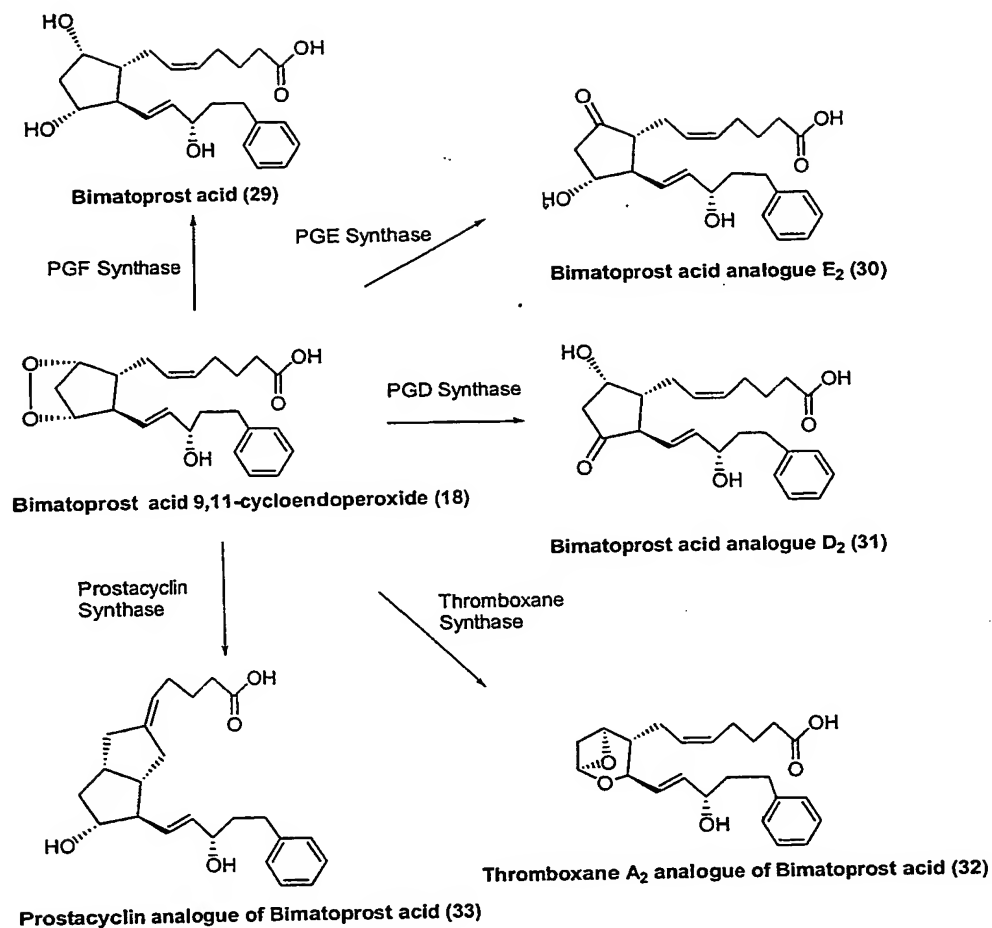
10 Enzymatic synthesis of Prostacyclin 1-ethanolamide (**Compound 28**)

11 Prostacyclin 1-ethanolamide is synthesized from prostaglandin H₂ 1-
12 ethanolamide 9,11-cycloendoperoxide (**Compound 17**) following General
13 Procedure E using the human recombinant prostacyclin synthase obtained
14 in accordance with the publication of *Miyata et al.*, Biochem. Biophys.
15 Res. Commun. 1994, 200: 1728-1734, instead of the human recombinant
16 PGF synthase, as illustrated in **Reaction Scheme 14**.

17 Enzymatic synthesis of Bimatoprost acid (**Compound 29**), its
18 prostaglandin analogues E₂ and D₂ (**Compounds 30-31**), thromboxane
19 analogue A₂ (**Compound 32**) and prostacyclin analogue (**Compound 33**)

20 **Compounds 29-33** are synthesized starting with Bimatoprost acid
21 9,11-cycloendoperoxide (**Compound 18**), instead of prostaglandin H₂ 1-
22 ethanolamide (**Compound 17**), following General Procedures E, F, G, H
23 and I, respectively, as illustrated in **Reaction Scheme 15** below.

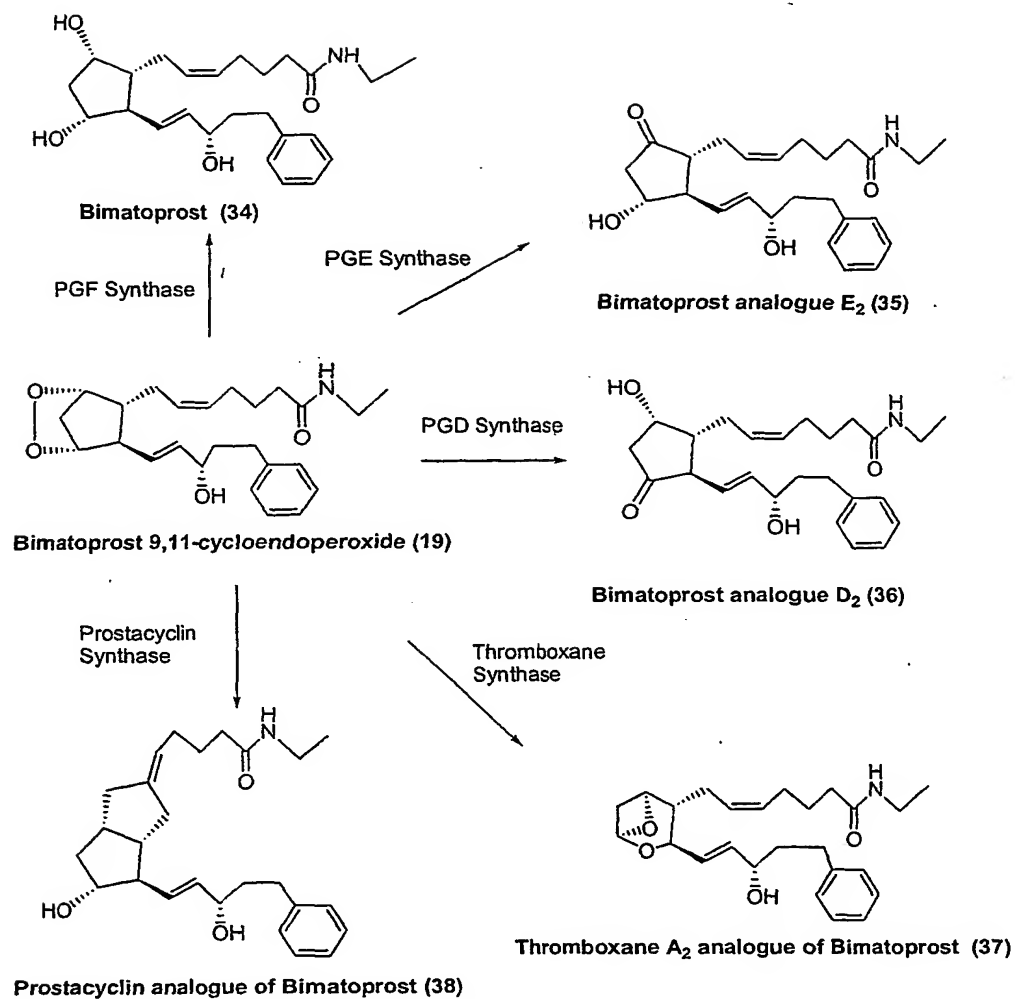
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REACTION SCHEME 15

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1 Enzymatic synthesis of Bimatoprost (Compound 34), its
2 prostaglandin analogues E₂ and D₂ (Compounds 35-36), thromboxane
3 analogue A₂ (Compound 37) and prostacyclin analogue (Compound 38)
4 **Compounds 34-38** are synthesized from Bimatoprost 9,11-
5 cycloendoperoxide (**Compound 19**), instead of prostaglandin H₂ 1-
6 ethanolamide (**Compound 17**), following General Procedures E, F, G, H
7 and I, respectively, as illustrated in **Reaction Scheme 16** below.
8



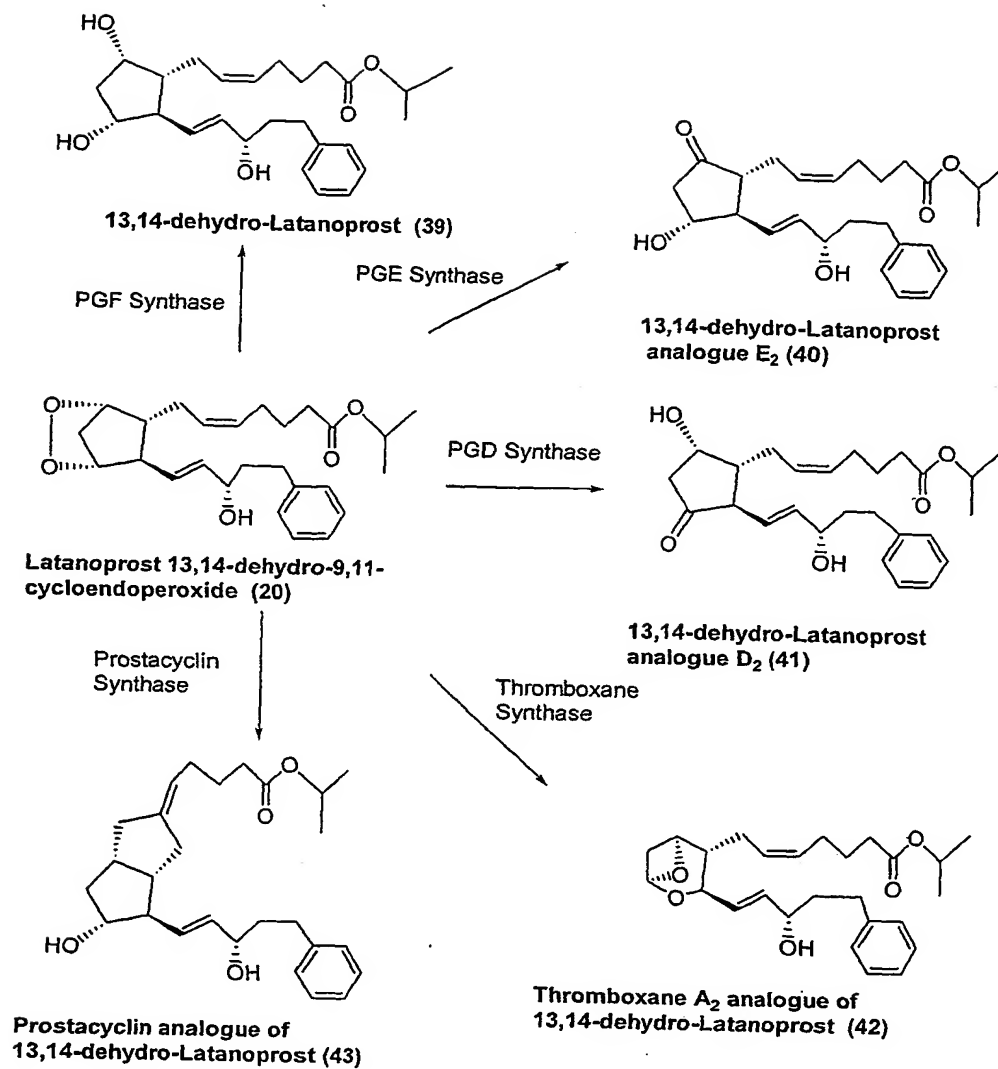
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REACTION SCHEME 16

1 Enzymatic synthesis of 13,14-dehydro-Latanoprost (Compound 39), its
2 prostaglandin analogues E₂ and D₂ (Compounds 40-41), thromboxane
3 analogue A₂ (Compound 42) and prostacyclin analogue (Compounds 43)

4 **Compounds 39-43** are synthesized from Latanoprost 13,14-dehydro-
5 9,11-cycloendoperoxide (**Compound 20**), instead of prostaglandin H₂ 1-
6 ethanolamide, (**Compound 17**) following General Procedures E, F, G, H
7 and I, respectively, as illustrated in **Reaction Scheme 17** below.

8



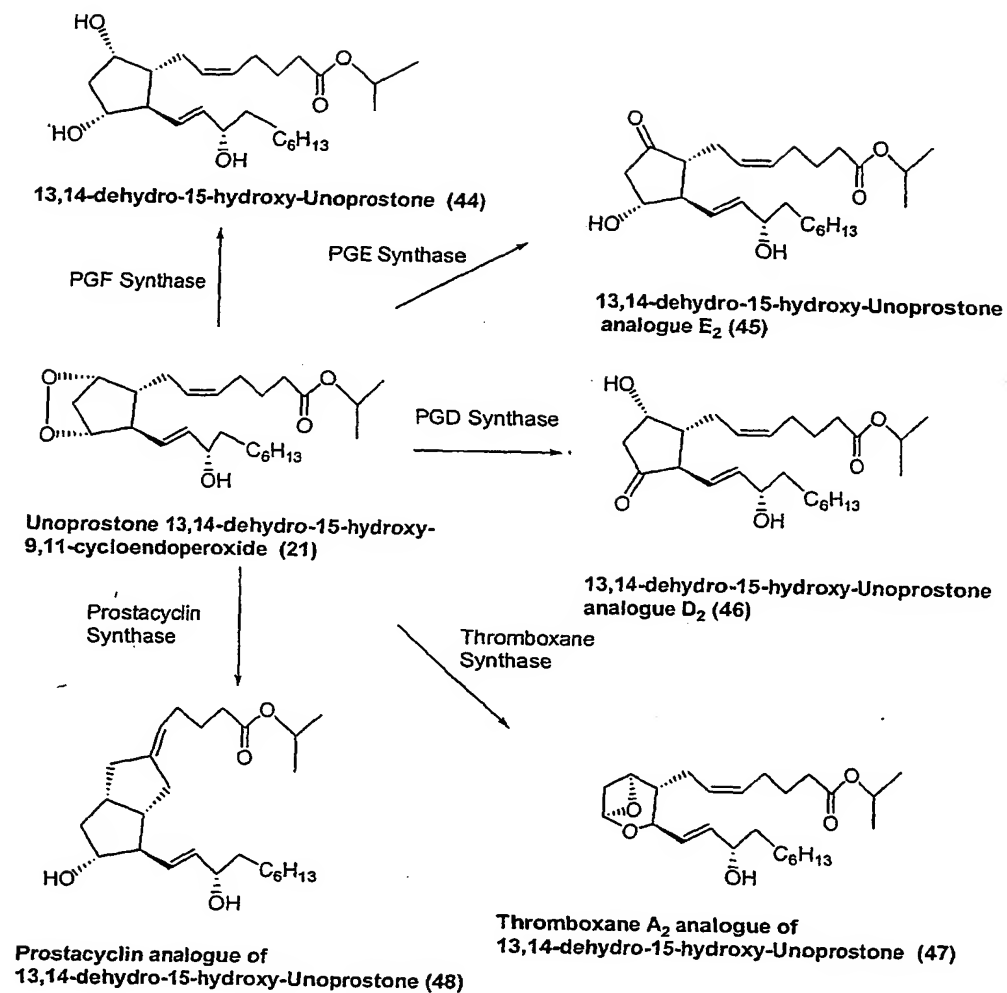
REACTION SCHEME 17

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1 Enzymatic synthesis of 13,14-dehydro-15-hydro-Unoprostone (Compound
2 44), its prostaglandin analogues E₂ and D₂ (Compounds 45-46),
3 thromboxane analogue A₂ (Compound 47) and prostacyclin analogue
4 (Compound 48)

5 **Compounds 44-48** are synthesized from Unoprostone 13,14-
6 dehydro-15-hydroxy-9,11-cycloendoperoxide (**Compound 21**), instead of
7 prostaglandin H₂ 1-ethanolamide (**Compound 17**), following General
8 Procedures E, F, G, H and I, respectively, as illustrated in **Reaction**
9 **Scheme 18** below.

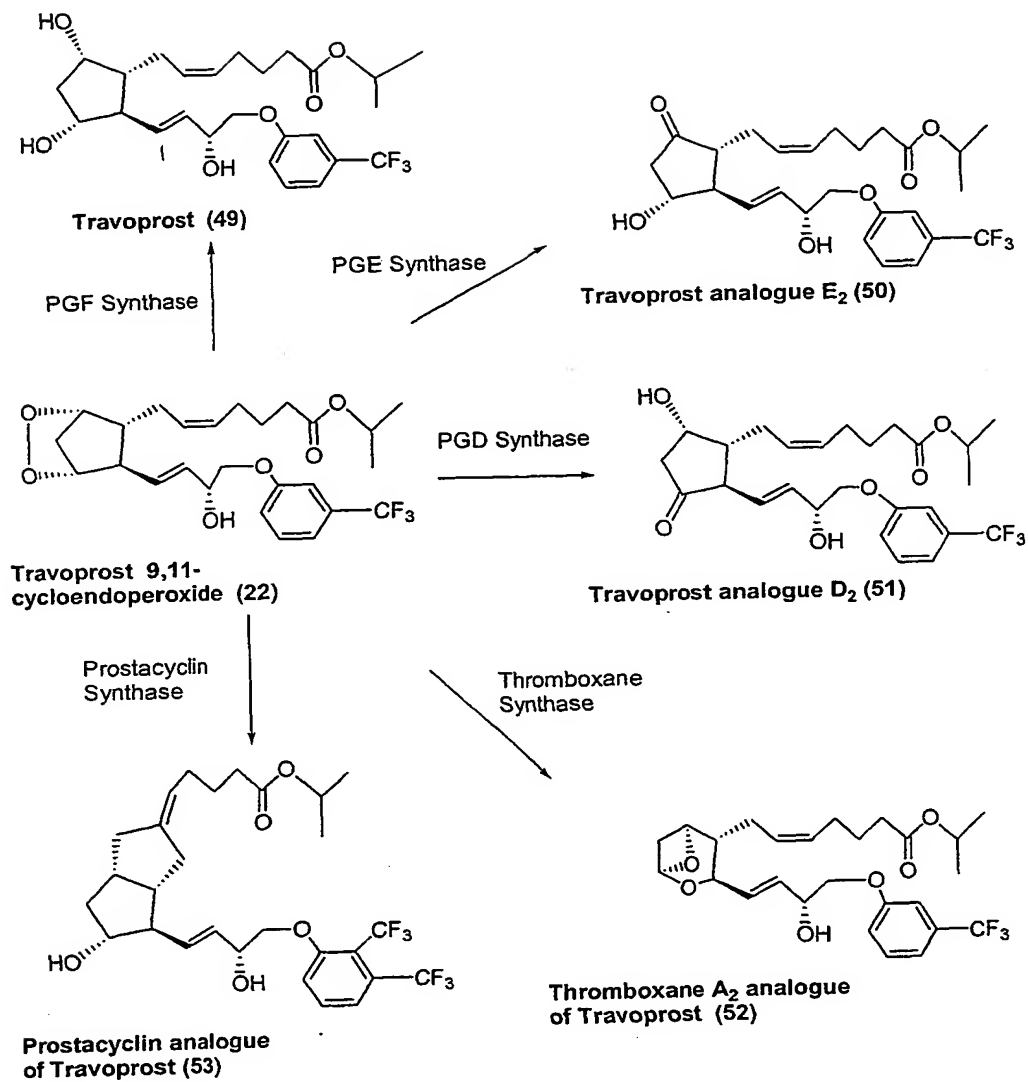
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REACTION SCHEME 18

1 Enzymatic synthesis of Travoprost (Compound 49), its prostaglandin
2 analogues E₂ and D₂ (Compounds 50-51), thromboxane analogue A₂
3 (Compound 52) and prostacyclin analogue (Compound 53) Compounds
4 49-53 are synthesized from Travoprost 9,11-cycloendoperoxide
5 (Compound 22), instead of prostaglandin H₂ 1-ethanolamide (Compound
6 17), following General Procedures E, F, G, H and I, respectively, as
7 illustrated in **Reaction Scheme 19** below.
8



REACTION SCHEME 19

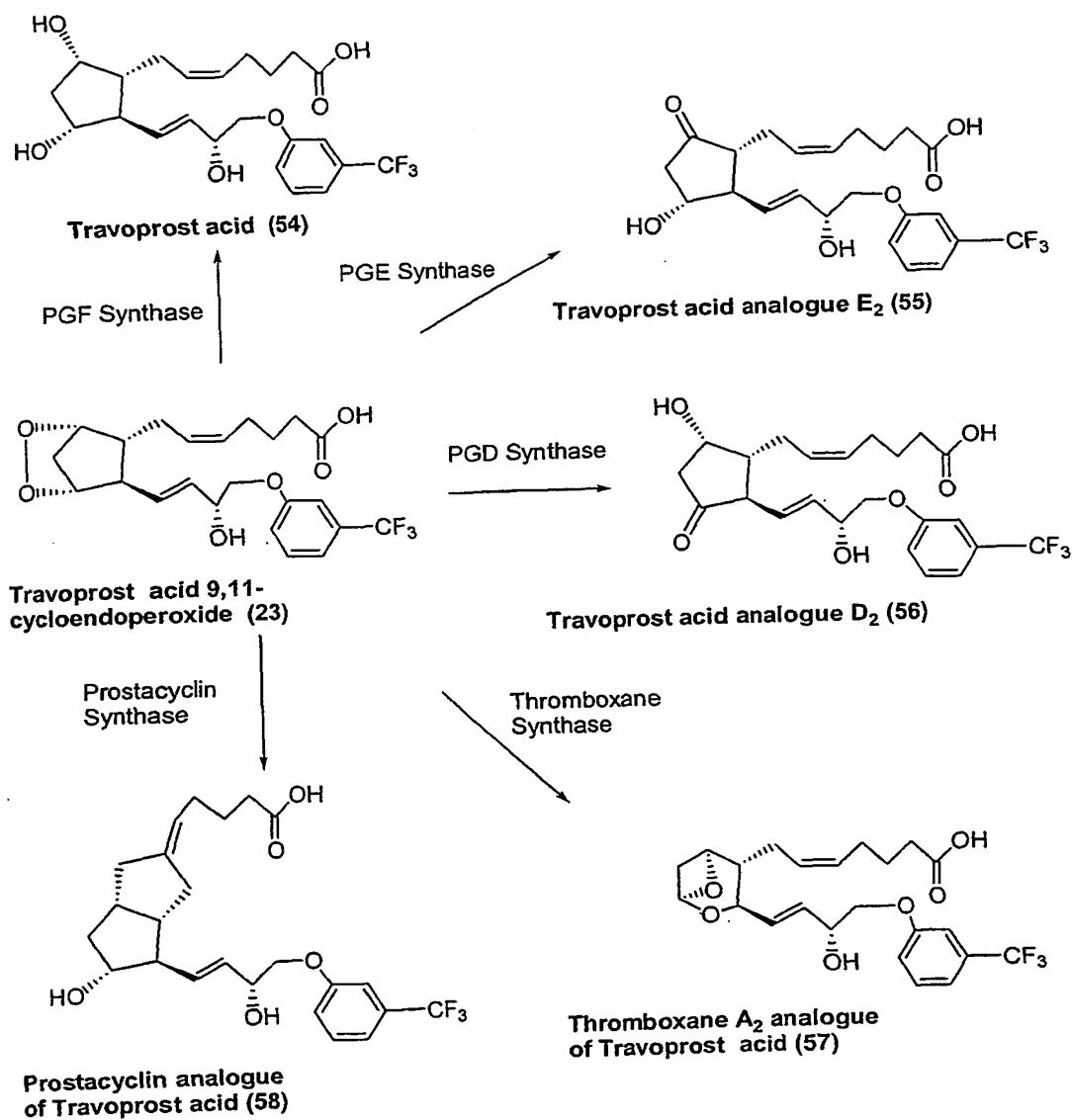
1 Enzymatic synthesis of Travoprost acid (Compound 54), its prostaglandin
2 analogues E₂ and D₂ (Compounds 55-56), thromboxane analogue A₂
3 (Compound 57) and prostacyclin analogue (Compounds 58)

4 **Compounds 54-58** are synthesized from Travoprost acid 9,11-
5 cycloendoperoxide (**Compound 23**), instead of prostaglandin H₂ 1-
6 ethanolamide (Compound 17), following General Procedures E, F, G, H
7 and I, respectively, as illustrated in **Reaction Scheme 20** below.

8

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REACTION SCHEME 20

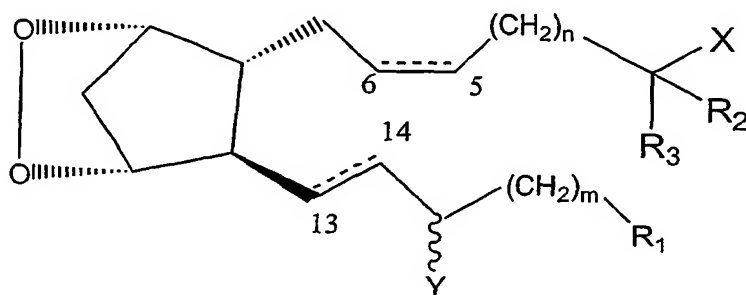
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WHAT IS CLAIMED IS:

1. A compound of the formula



wherein the dashed lines represent the presence of a bond, or absence of a bond, wavy lines represent either alpha or beta configuration, solid triangles represent beta configuration and hatched lines represent alpha configuration;

n is an integer having the values of 1 to 6;

m is an integer having the values of 1 to 8;

X is NH_2 , $N(R)_2$, NHR , or OR where R is hydrogen, R_4 or a $--(CO)R_4$ group;

Y is $=O$, $=S$ or OH , OR_5 or $--O(CO)R_5$ groups, said OH , OR_5 or $O(CO)R_5$ groups being attached to the adjacent carbon in alpha or beta configuration;

R_1 is H , CH_3 , R_7 , OR_7 or SR_7 where R_7 is an aliphatic, aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms selected from O , S , and N , said aliphatic, aromatic or heteroaromatic ring being optionally substituted with 1 to 3 R_8 groups where R_8 is F , Cl , Br , I , NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, $COOH$, or $COOR_9$ where R_9 is alkyl of 1 to 6 carbons or CH_2OCH_3 ;

R_2 and R_3 together represent $=O$, $=S$, or independently are hydrogen or alkyl of 1 to 6 carbon atoms;

- 1 R_4 represents $(CH_2)_rOH$, $(CH_2)_rOCOR_9$ or $(CH_2)_rOR_9$ where r is an integer
2 having the values 1 to 6, or R_4 represents saturated or unsaturated acyclic
3 hydrocarbons having from 1 to 20 carbon atoms, or $-(CH_2)_qR_6$ where q is
4 0-10 and R_6 is an aliphatic, aromatic or heteroaromatic ring, said
5 heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N,
6 said aliphatic, aromatic or heteroaromatic ring being optionally substituted
7 with 1 to R_8 groups where R_8 is F, Cl, Br, I, NO_2 , C_{1-6} alkyl, C_{1-6} fluoro
8 substituted alkyl, $COOH$, $COOR_9$ where R_9 is alkyl of 1 to 6 carbons or
9 CH_2OCH_3 ;
10 R_5 represents saturated or unsaturated acyclic hydrocarbons having from 1
11 to 20 carbon atoms, or $-(CH_2)_qR_6$, or a pharmaceutically acceptable salt of
12 said compound.
13 2. A compound in accordance with Claim 1 where n is 3.
14 3. A compound in accordance with Claim 1 where m is an integer having
15 the values 1 to 6.
16 4. A compound in accordance with Claim 1 where the dotted line between
17 the carbons designated 13 and 14 represents a bond.
18 5. A compound in accordance with Claim 1 where the dotted line between
19 the carbons designated 13 and 14 represents absence of a bond.
20 6. A compound in accordance with Claim 1 where the dotted line between
21 the carbons designated 5 and 6 represents a bond.
22 7. A compound in accordance with Claim 1 where Y is $=O$ or OH , or
23 $O(CO)R_5$, where R_5 is alkyl of 1 to 6 carbons.
24 8. A compound in accordance with Claim 1 where Y is OH attached to the
25 adjacent carbon by a bond of alpha orientation.
26 9. A compound in accordance with Claim 1 where R_1 is methyl, phenyl, O-
27 phenyl, phenyl substituted with 1 to 3 R_8 groups, or O-phenyl substituted
28 with 1 to 3 R_8 groups.
29 10. A compound in accordance with Claim 1 where R_2 and R_3 jointly form

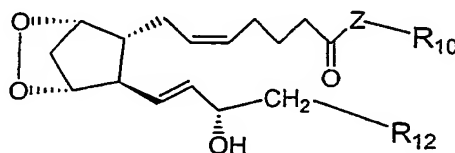
1 an oxo (=O) group.

2 11. A compound in accordance with Claim 9 where OH, OR₄ or NHR₄ or
3 OR₄.

4 12. A compound in accordance with Claim 10 where R₄ is alkyl of 1 to 6
5 carbons, or (CH₂)_rOH.

6 13. A compound having the formula

7



8

9

10 where Z is O or NH;

11 R₁₀ is H, R₁₁ or (CH₂)₂OH;

12 R₁₁ is alkyl of 1 to 3 carbons, and

13 R₁₂ is selected from the group consisting of *n*-butyl, *n*-hexyl, CH₂-phenyl
14 and O-(3-trifluoromethyl)phenyl.

15 14. A compound in accordance with Claim 13 where Z is O.

16 15. A compound in accordance with Claim 13 where Z is NH.

17 16. A compound in accordance with Claim 13 where R₁₀ is H.

18 17. A compound in accordance with Claim 13 where R₁₀ is ethyl.

19 18. A compound in accordance with Claim 13 where R₁₀ is *iso*-propyl.

20 19. A compound in accordance with Claim 13 where R₁₀ is CH₂CH₂OH.

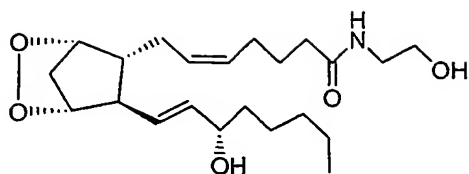
21 20. A compound in accordance with Claim 13 where R₁₂ is *n*-butyl.

22 21. A compound in accordance with Claim 13 where R₁₂ is *n*-hexyl.

23 22. A compound in accordance with Claim 13 where R₁₂ is CH₂-phenyl.

24 23. A compound in accordance with Claim 13 where R₁₂ is O-(3-
25 trifluoromethyl)phenyl.

26 24. A compound in accordance with Claim 13, having the formula

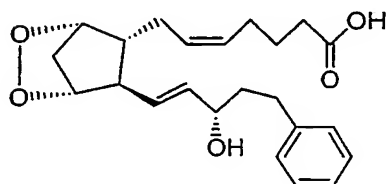


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3 **25.** A compound in accordance with Claim 13, having the formula

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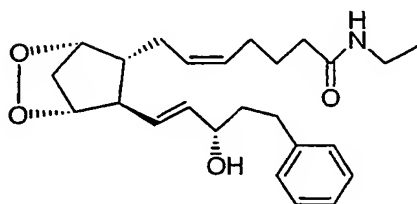


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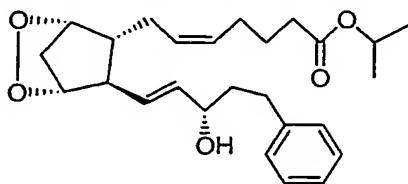
7 **26.** A compound in accordance with Claim 13, having the formula

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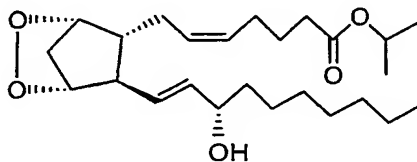
11 **27.** A compound in accordance with Claim 13, having the formula

12

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14 **28.** A compound in accordance with Claim 13, having the formula

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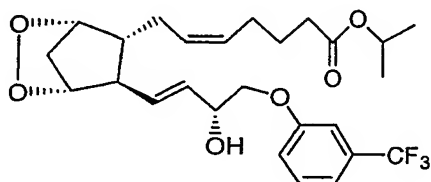


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1 **29.** A compound in accordance with Claim 13, having the formula

2

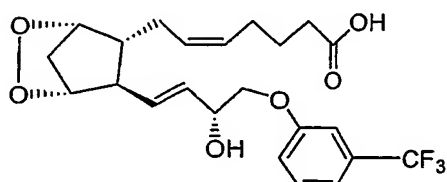


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5 **30.** A compound in accordance with Claim 13, having the formula

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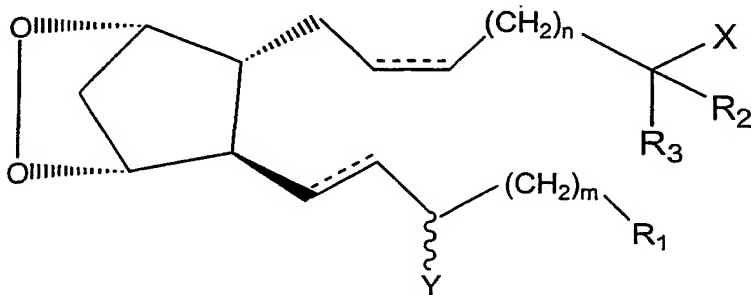


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9 **31.** A pharmaceutical composition adapted for administration to a
10 mammal, the composition comprising a pharmaceutically acceptable
11 excipient and a compound of the formula

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15 wherein the dashed lines represent the presence of a bond, or absence of a
16 bond, wavy lines represent either alpha or beta configuration, solid triangles
17 represent beta configuration and hatched lines represent alpha
18 configuration;

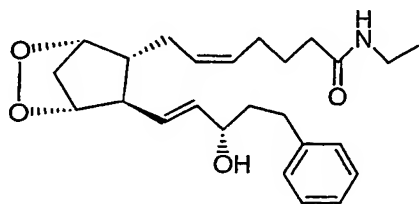
19 **n** is an integer having the values of 1 to 6;

20 **m** is an integer having the values of 1 to 8;

- 1 X is NH_2 , $\text{N}(\text{R})_2$, NHR , or OR where R is hydrogen, R_4 or a $-(\text{CO})\text{R}_4$
2 group;
3 Y is $=\text{O}$, $=\text{S}$ or OH , OR_5 or $-\text{O}(\text{CO})\text{R}_5$ groups, said OH , OR_5 or $\text{O}(\text{CO})\text{R}_5$
4 groups being attached to the adjacent carbon in alpha or beta configuration;
5 R_1 is H , CH_3 , R_7 , OR_7 or SR_7 where R_7 is an aliphatic, aromatic or
6 heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms
7 selected from O, S, and N, said aliphatic, aromatic or heteroaromatic ring
8 being optionally substituted with 1 to 3 R_8 groups where R_8 is F, Cl, Br, I,
9 NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, COOH , or COOR_9 where R_9
10 is alkyl of 1 to 6 carbons or CH_2OCH_3 ;
11 R_2 and R_3 together represent $=\text{O}$, $=\text{S}$, or independently are hydrogen or
12 alkyl of 1 to 6 carbon atoms;
13 R_4 represents $(\text{CH}_2)_r\text{OH}$, $(\text{CH}_2)_r\text{OCOR}_9$ or $(\text{CH}_2)_r\text{OR}_9$ where r is an integer
14 having the values 1 to 6, or R_4 represents saturated or unsaturated acyclic
15 hydrocarbons having from 1 to 20 carbon atoms, or $-(\text{CH}_2)_q\text{R}_6$ where q is
16 0-10 and R_6 is an aliphatic, aromatic or heteroaromatic ring, said
17 heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N,
18 said aliphatic, aromatic or heteroaromatic ring being optionally substituted
19 with 1 to R_8 groups where R_8 is F, Cl, Br, I, NO_2 , C_{1-6} alkyl, C_{1-6} fluoro
20 substituted alkyl, COOH , COOR_9 where R_9 is alkyl of 1 to 6 carbons or
21 CH_2OCH_3 ;
22 R_5 represents saturated or unsaturated acyclic hydrocarbons having from 1
23 to 20 carbon atoms, or $-(\text{CH}_2)_q\text{R}_6$, or a pharmaceutically acceptable salt of
24 said compound.
25 32. A pharmaceutical composition in accordance with Claim 31 which is
26 adapted for administration to a mammal to decrease intraocular pressure in
27 the eye of the mammal.
28 33. A pharmaceutical composition in accordance with Claim 32 wherein

1 the compound is selected from the group consisting of compounds having
2 the formulas (i) through (vii)

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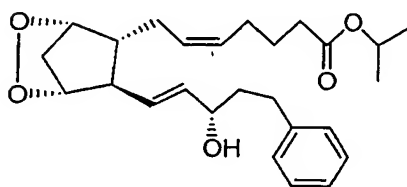
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(i)

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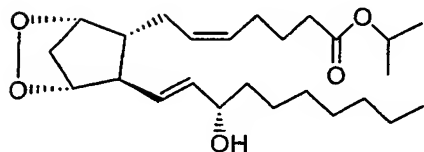


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(ii)

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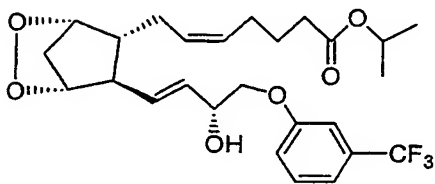
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(iii)

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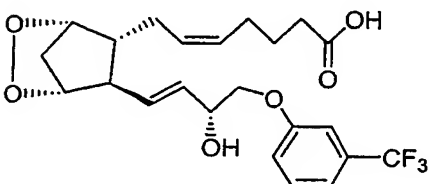


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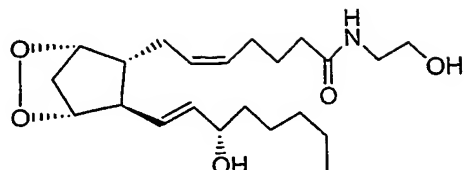


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(v)

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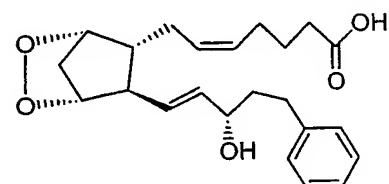


(vi)

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(vii)

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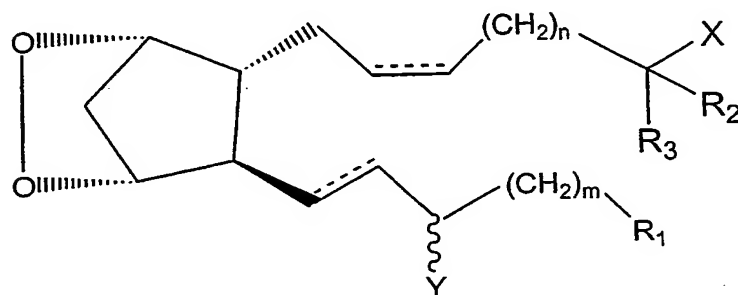
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8 34. A pharmaceutical composition in accordance with Claim 32 adapted
9 for topical administration to the mammalian eye.

10 35. A method of administering a pro-drug to a mammal in need of such
11 administration, the pro-drug comprising a compound of the formula

12



13

14 wherein the dashed lines represent the presence of a bond, or absence of a
15 bond, wavy lines represent either alpha or beta configuration, solid triangles
16 represent beta configuration and hatched lines represent alpha
17 configuration;

18 **n** is an integer having the values of 1 to 6;

19 **m** is an integer having the values of 1 to 8;

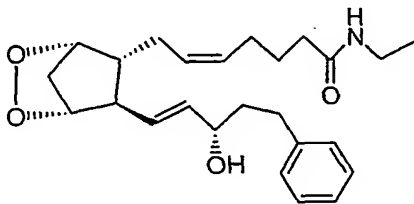
20 **X** is NH_2 , N(R)_2 , NHR , or OR where **R** is hydrogen, R_4 or a --(CO)R_4
21 group;

22 **Y** is $=\text{O}$, $=\text{S}$ or OH , OR_5 or --O(CO)R_5 groups, said OH , OR_5 or O(CO)R_5

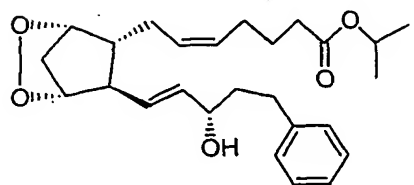
23 groups being attached to the adjacent carbon in alpha or beta configuration;

1 R_1 is H, CH_3 , R_7 , OR_7 or SR_7 where R_7 is an aliphatic, aromatic or
2 heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms
3 selected from O, S, and N, said aliphatic, aromatic or heteroaromatic ring
4 being optionally substituted with 1 to 3 R_8 groups where R_8 is F, Cl, Br, I,
5 NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, $COOH$, or $COOR_9$ where R_9
6 is alkyl of 1 to 6 carbons or CH_2OCH_3 ;
7 R_2 and R_3 together represent $=O$, $=S$, or independently are hydrogen or
8 alkyl of 1 to 6 carbon atoms;
9 R_4 represents $(CH_2)_rOH$, $(CH_2)_rOCOR_9$ or $(CH_2)_rOR_9$ where r is an integer
10 having the values 1 to 6, or R_4 represents saturated or unsaturated acyclic
11 hydrocarbons having from 1 to 20 carbon atoms, or $-(CH_2)_qR_6$ where q is
12 0-10 and R_6 is an aliphatic, aromatic or heteroaromatic ring, said
13 heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N,
14 said aliphatic, aromatic or heteroaromatic ring being optionally substituted
15 with 1 to R_8 groups where R_8 is F, Cl, Br, I, NO_2 , C_{1-6} alkyl, C_{1-6} fluoro
16 substituted alkyl, $COOH$, $COOR_9$ where R_9 is alkyl of 1 to 6 carbons or
17 CH_2OCH_3 ;
18 R_5 represents saturated or unsaturated acyclic hydrocarbons having from 1
19 to 20 carbon atoms, or $-(CH_2)_qR_6$, or a pharmaceutically acceptable salt of
20 said compound.

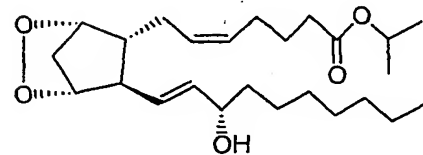
- 1 36. A method in accordance with Claim 35 wherein the pro-drug is
2 administered to decrease intraocular pressure in the eye of the mammal.
3 37. A method in accordance with Claim 36 wherein the compound is
4 selected from the group consisting of compounds having the formulas (i)
5 through (vii)
6



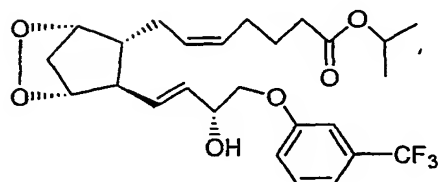
(i)



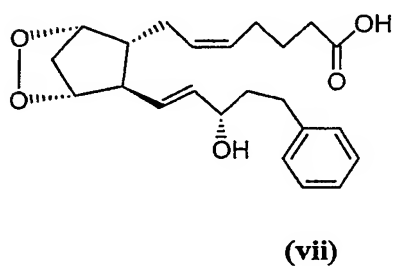
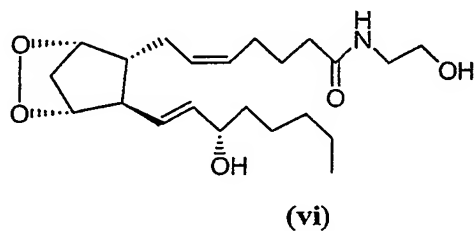
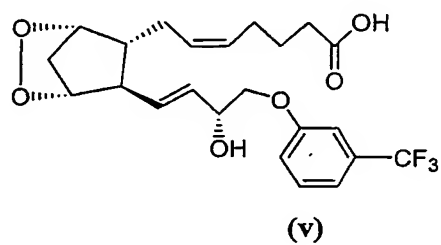
(ii)



(iii)



(iv)



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11 38. A method in accordance with Claim 37 wherein the pro-drug is
12 administered topically to decrease intraocular pressure in the eye of the
13 mammal.

14

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/24305

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D317/06 A61K31/357 A61P27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAZ, AMIRAM ET AL: "Endoperoxides and thromboxanes. Structural determinants for platelet aggregation and vasoconstriction" BIOCHIMICA ET BIOPHYSICA ACTA (1977), 488(2), 305-11 , XP008025412 figure 3	1, 31
X	WO 02 12445 A (UNIV VANDERBILT) 14 February 2002 (2002-02-14) fig. 7 and 8, PGH2-EA --- -/-	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

22 December 2003

Date of mailing of the international search report

08/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/24305

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35-38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/24305

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GORMAN R R ET AL: "PROSTAGLANDIS H1 AND H2. CONVENIENT BIOCHEMICAL SYNTHESIS AND ISOLATION. FURTHER BIOLOGICAL AND SPECTROSCOPIC CHARACTERIZATION"</p> <p>PROSTAGLANDINS, BUTTERWORTH, STONEHAM, MA, US,</p> <p>vol. 13, no. 6, June 1977 (1977-06), pages 1043-1053, XP001160973</p> <p>ISSN: 0090-6980</p> <p>page 1044 -page 1046; table 1</p> <p>----</p>	1
X	<p>GRAFF, G. ET AL: "Identification of 15-keto-9,11-peroxidoprostanoic acid as a hematin-catalyzed decomposition product of 15-hydroperoxy-9,11-peroxidoprostanoic acid"</p> <p>LIPIDS (1979), 14(4), 334-42 ,</p> <p>XP008025451</p> <p>figure 7</p> <p>----</p>	1
X	<p>DICZFALUSY, ULF ET AL: "Enzymic conversion of C21 endoperoxides to thromboxanes and hydroxy acids"</p> <p>BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS (1980), 94(4), 1417-23 ,</p> <p>XP008025450</p> <p>figure 4</p> <p>----</p>	1
X	<p>LEDUC, LOUISE E. ET AL: "Analogues of arachidonic acid used to evaluate structural determinants of prostaglandin receptor and enzyme specificities"</p> <p>MOLECULAR PHARMACOLOGY (1981), 19(2), 242-7 ,</p> <p>XP008025459</p> <p>table 2</p> <p>-----</p>	1

INTERNATIONAL SEARCH REPORT

in on patent family members

International Application No

PCT/US 03/24305

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0212445	A	14-02-2002	
		AU 8474701 A	18-02-2002
		AU 8475301 A	18-02-2002
		CA 2422306 A1	14-02-2002
		CA 2422803 A1	14-02-2002
		EP 1307585 A1	07-05-2003
		EP 1307538 A1	07-05-2003
		WO 0212549 A1	14-02-2002
		WO 0212445 A1	14-02-2002
		US 2002064804 A1	30-05-2002
		US 2002106707 A1	08-08-2002

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/013119 A1

(51) International Patent Classification⁷: **C07D 317/06**,
A61K 31/357, A61P 27/00

(21) International Application Number:
PCT/US2003/024305

(22) International Filing Date: 4 August 2003 (04.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/212,437 5 August 2002 (05.08.2002) US

(71) Applicant: **ALLERGAN, INC.** [US/US]; 2525 Dupont
Drive, Irvine, CA 92612 (US).

(72) Inventors: **LING, Kah-Hiing, John**; 82 Lessay, Newport
Coast, CA 92657 (US). **YANG, Wu**; 1 Corte Trovata,
Irvine, CA 92606 (US). **NI, Jinsong**; 9 Coca, Foothill
Ranch, CA 92610 (US). **YUAN, Haiqing**; 28 Del Trevi,
Irvine, CA 92606 (US). **TANG-LIU, Diane, D., S.**; 2615
Blackthorn Street, Newport Beach, CA 92660 (US).

(74) Agents: **FISHER, Carlos, A. et al.**; c/o Allergan, Inc.,
2525 Dupont Drive, Irvine, CA 92612 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

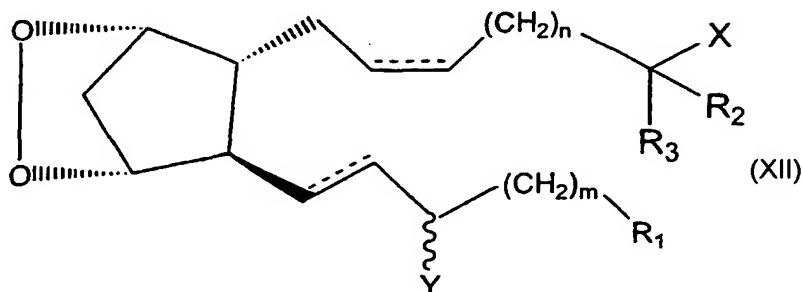
- with international search report
- with amended claims and statement

Date of publication of the amended claims and statement:

6 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THE 9, 11-CYCLOENDOPEROXIDE PRO-DRUGS OF PROSTAGLANDIN ANALOGUES FOR TREATMENT OF OCULAR HYPERTENSION AND GLAUCOMA



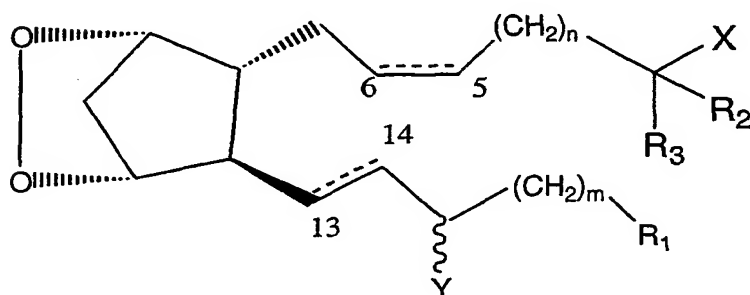
(57) Abstract: 9,11-Cycloendoperoxide derivatives of biologically active prostaglandin analogs, and particularly of the ocular hypotensive drugs Bimatoprost, Latanoprost, Unoprostone, Travoprost and prostaglandin H₂ 1-ethanolamide or of structurally closely related analogs, are pro-drugs which hydrolyze under physiological conditions to provide prostaglandin analogues that are capable of providing sustained ocular and other in vivo concentrations of the respective drugs. The compounds of

the invention have the formula shown below where the variables have the meaning defined in the specification.

AMENDED CLAIMS

[Received by the International Bureau on 01 March 2004 (01.03.04):
original claims 1-38 replaced by amended claims bearing the same
numbers (12 pages)]

1. (currently amended) A compound of the formula



wherein the dashed lines represent the presence of a bond, or absence of a bond, wavy lines represent either alpha or beta configuration, solid triangles represent beta configuration and hatched lines represent alpha configuration;
n is an integer having the values of 1 to 6;

m is an integer having the values of 1 to 8;

X is NH_2 , N(R)_2 , NHR , or OR where **R** is hydrogen, R_4 or a --(CO)R_4 group;

Y is $=\text{S}$ or OH , OR_5 or --O(CO)R_5 groups, said OH , OR_5 or O(CO)R_5 groups being attached to the adjacent carbon in alpha or beta configuration;

R₁ is H , CH_3 , R_7 , OR_7 or SR_7 where **R₇** is an aliphatic, aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms selected from O , S , and N , said aliphatic, aromatic or heteroaromatic ring being optionally substituted with 1 to 3 **R₈** groups where **R₈** is F , Cl , Br , I , NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, COOH , or COOR_9 where **R₉** is alkyl of 1 to 6 carbons or CH_2OCH_3 ;

R₂ and **R₃** together represent $=\text{O}$, $=\text{S}$, or independently are hydrogen or alkyl of 1 to 6 carbon atoms, with the proviso that when **X** is OR then **R₁** is not H nor methyl;

R_4 represents $(CH_2)_rOH$, $(CH_2)_rOCOR_9$ or $(CH_2)_rOR_9$ where r is an integer having the values 1 to 6, or R_4 represents saturated or unsaturated acyclic hydrocarbons having from 1 to 20 carbon atoms, or $-(CH_2)_qR_6$ where q is 0-10 and R_6 is an aliphatic, aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N, said aliphatic, aromatic or heteroaromatic ring being optionally substituted with 1 to R_8 groups where R_8 is F, Cl, Br, I, NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, $COOH$, $COOR_9$ where R_9 is alkyl of 1 to 6 carbons or CH_2OCH_3 with the further proviso that when X is NHR , m is 4 and R_1 is methyl then R_4 is not $(CH_2)_2OH$;

R_5 represents saturated or unsaturated acyclic hydrocarbons having from 1 to 20 carbon atoms, or $-(CH_2)_qR_6$, or a pharmaceutically acceptable salt of said compound.

2. A compound in accordance with Claim 1 where n is 3.
3. A compound in accordance with Claim 1 where m is an integer having the values 1 to 6.
4. A compound in accordance with Claim 1 where the dotted line between the carbons designated 13 and 14 represents a bond.
5. A compound in accordance with Claim 1 where the dotted line between the carbons designated 13 and 14 represents absence of a bond.
6. A compound in accordance with Claim 1 where the dotted line between the carbons designated 5 and 6 represents a bond.
7. A compound in accordance with Claim 1 where Y is $=O$ or OH , or $O(CO)R_5$, where R_5 is alkyl of 1 to 6 carbons.
8. A compound in accordance with Claim 1 where Y is OH attached to the adjacent carbon by a bond of alpha orientation.
9. A compound in accordance with Claim 1 where R_1 is methyl, phenyl, O-

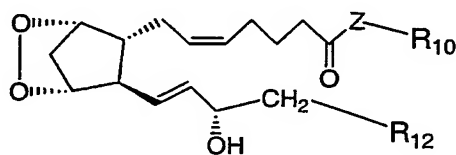
phenyl, phenyl substituted with 1 to 3 R_8 groups, or O-phenyl substituted with 1 to 3 R_8 groups.

10. A compound in accordance with Claim 1 where R_2 and R_3 jointly form an oxo (=O) group.

11. (currently amended) A compound in accordance with Claim 9 where X is OH, OR_4 or NHR_4 .

12. A compound in accordance with Claim 10 where R_4 is alkyl of 1 to 6 carbons, or $(CH_2)_rOH$.

13. (currently amended) A compound having the formula



where Z is O or NH;

R_{10} is H, R_{11} or $(CH_2)_2OH$;

R_{11} is alkyl of 1 to 3 carbons, and

R_{12} is selected from the group consisting of *n*-butyl, *n*-hexyl, CH_2 -phenyl and O-(3-trifluoromethyl)phenyl with the proviso that when Z is O and R_{12} is *n*-butyl then R_{10} is not H nor R_{11} , with the further proviso that when Z is NH and R_{12} is *n*-butyl then R_{10} is not $(CH_2)_2OH$.

14. A compound in accordance with Claim 13 where Z is O.

15. A compound in accordance with Claim 13 where Z is NH.

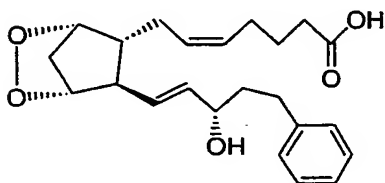
16. A compound in accordance with Claim 13 where R_{10} is H.

17. A compound in accordance with Claim 13 where R_{10} is ethyl.

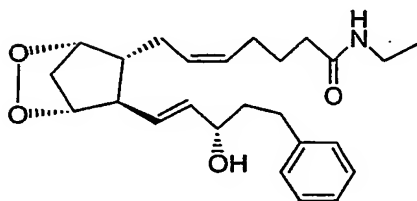
18. A compound in accordance with Claim 13 where R_{10} is *iso*-propyl.

19. A compound in accordance with Claim 13 where R_{10} is CH_2CH_2OH .

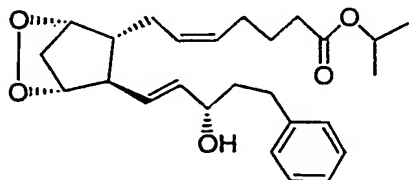
20. A compound in accordance with Claim 13 where R_{12} is *n*-butyl.
21. A compound in accordance with Claim 13 where R_{12} is *n*-hexyl.
22. A compound in accordance with Claim 13 where R_{12} is CH_2 -phenyl.
23. A compound in accordance with Claim 13 where R_{12} is O-(3-trifluoromethyl)phenyl.
24. (canceled)
25. A compound in accordance with Claim 13, having the formula



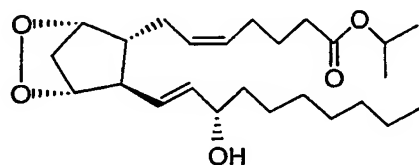
26. A compound in accordance with Claim 13, having the formula



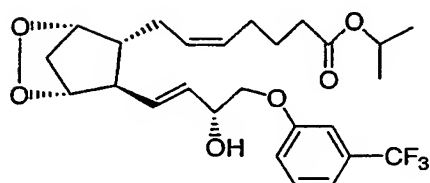
27. A compound in accordance with Claim 13, having the formula



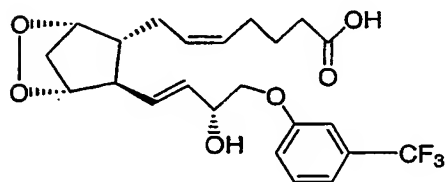
28. A compound in accordance with Claim 13, having the formula



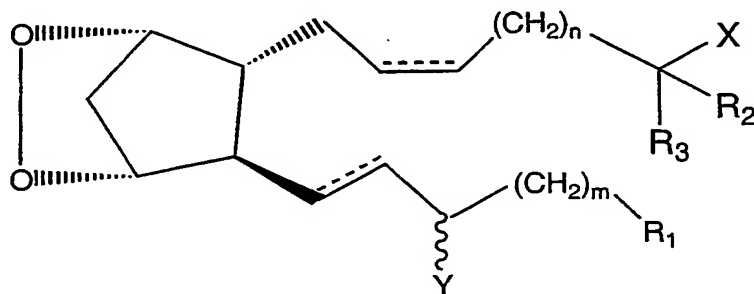
29. A compound in accordance with Claim 13, having the formula



30. A compound in accordance with Claim 13, having the formula



31. A pharmaceutical composition adapted for administration to a mammal, the composition comprising a pharmaceutically acceptable excipient and a compound of the formula



wherein the dashed lines represent the presence of a bond, or absence of a bond, wavy lines represent either alpha or beta configuration, solid triangles represent beta configuration and hatched lines represent alpha configuration; n is an integer having the values of 1 to 6;

m is an integer having the values of 1 to 8;

X is NH_2 , $\text{N}(\text{R})_2$, NHR , or OR where R is hydrogen, R_4 or a $-(\text{CO})\text{R}_4$ group;

Y is $=\text{O}$, $=\text{S}$ or OH , OR_5 or $-(\text{CO})\text{R}_5$ groups, said OH , OR_5 or $\text{O}(\text{CO})\text{R}_5$ groups being attached to the adjacent carbon in alpha or beta configuration;

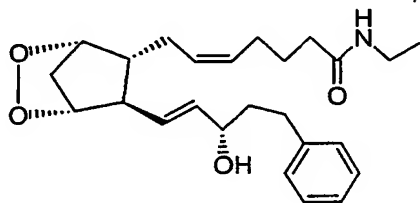
R_1 is H , CH_3 , R_7 , OR_7 or SR_7 where R_7 is an aliphatic, aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N, said aliphatic, aromatic or heteroaromatic ring being optionally substituted with 1 to 3 R_8 groups where R_8 is F, Cl, Br, I, NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, COOH , or COOR_9 where R_9 is alkyl of 1 to 6 carbons or CH_2OCH_3 ;

R_2 and R_3 together represent $=\text{O}$, $=\text{S}$, or independently are hydrogen or alkyl of 1 to 6 carbon atoms;

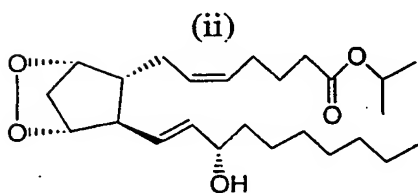
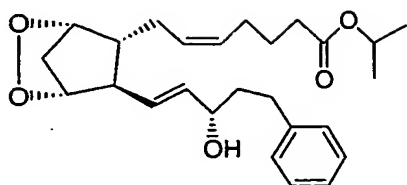
R_4 represents $(CH_2)_rOH$, $(CH_2)_rOCOR_9$ or $(CH_2)_rOR_9$ where r is an integer having the values 1 to 6, or R_4 represents saturated or unsaturated acyclic hydrocarbons having from 1 to 20 carbon atoms, or $-(CH_2)_qR_6$ where q is 0-10 and R_6 is an aliphatic, aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N, said aliphatic, aromatic or heteroaromatic ring being optionally substituted with 1 to R_8 groups where R_8 is F, Cl, Br, I, NO_2 , C_{1-6} alkyl, C_{1-6} fluoro substituted alkyl, $COOH$, $COOR_9$ where R_9 is alkyl of 1 to 6 carbons or CH_2OCH_3 ;
 R_5 represents saturated or unsaturated acyclic hydrocarbons having from 1 to 20 carbon atoms, or $-(CH_2)_qR_6$, or a pharmaceutically acceptable salt of said compound.

32. A pharmaceutical composition in accordance with Claim 31 which is adapted for administration to a mammal to decrease intraocular pressure in the eye of the mammal.

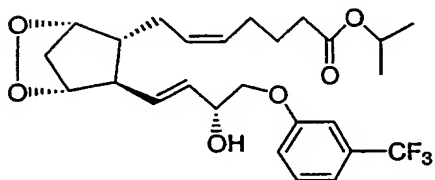
33. A pharmaceutical composition in accordance with Claim 32 wherein the compound is selected from the group consisting of compounds having the formulas (i) through (vii)



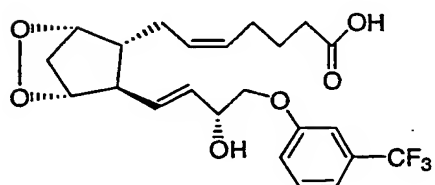
(i)



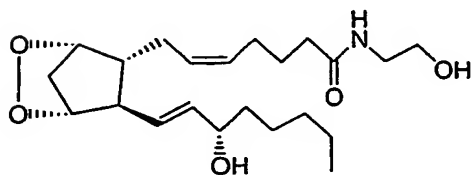
(iii)



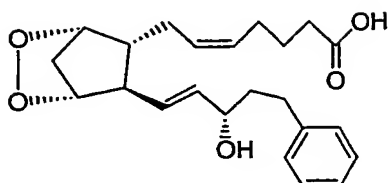
(iv)



(v)



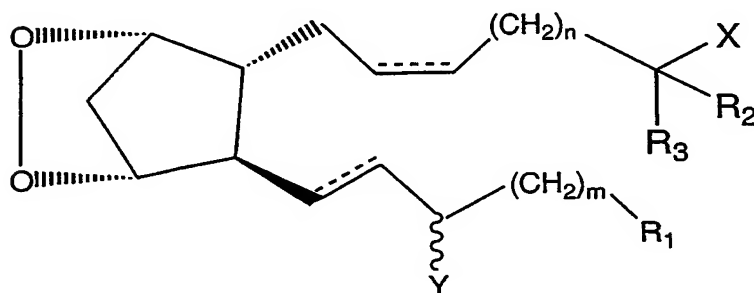
(vi)



(vii)

34. A pharmaceutical composition in accordance with Claim 32 adapted for topical administration to the mammalian eye.

35. A method of administering a pro-drug to a mammal in need of such administration, the pro-drug comprising a compound of the formula



wherein the dashed lines represent the presence of a bond, or absence of a bond, wavy lines represent either alpha or beta configuration, solid triangles represent beta configuration and hatched lines represent alpha configuration; n is an integer having the values of 1 to 6;

m is an integer having the values of 1 to 8;

X is NH_2 , $N(R)_2$, NHR , or OR where R is hydrogen, R_4 or a $-(CO)R_4$ group;

Y is =O, =S or OH, OR₅ or --O(CO)R₅ groups, said OH, OR₅ or O(CO)R₅ groups being attached to the adjacent carbon in alpha or beta configuration; R₁ is H, CH₃, R₇, OR₇ or SR₇ where R₇ is an aliphatic, aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N, said aliphatic, aromatic or heteroaromatic ring being optionally substituted with 1 to 3 R₈ groups where R₈ is F, Cl, Br, I, NO₂, C₁₋₆ alkyl, C₁₋₆ fluoro substituted alkyl, COOH, or COOR₉ where R₉ is alkyl of 1 to 6 carbons or CH₂OCH₃;

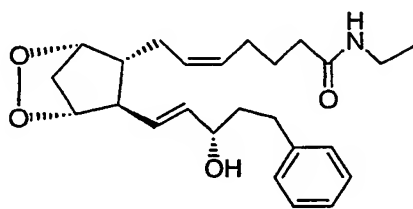
R₂ and R₃ together represent =O, =S, or independently are hydrogen or alkyl of 1 to 6 carbon atoms;

R₄ represents (CH₂)_rOH, (CH₂)_rOCOR₉ or (CH₂)_rOR₉ where r is an integer having the values 1 to 6, or R₄ represents saturated or unsaturated acyclic hydrocarbons having from 1 to 20 carbon atoms, or --(CH₂)_qR₆ where q is 0-10 and R₆ is an aliphatic, aromatic or heteroaromatic ring, said heteroaromatic ring having 1 to 3 heteroatoms selected from O, S, and N, said aliphatic, aromatic or heteroaromatic ring being optionally substituted with 1 to R₈ groups where R₈ is F, Cl, Br, I, NO₂, C₁₋₆ alkyl, C₁₋₆ fluoro substituted alkyl, COOH, COOR₉ where R₉ is alkyl of 1 to 6 carbons or CH₂OCH₃;

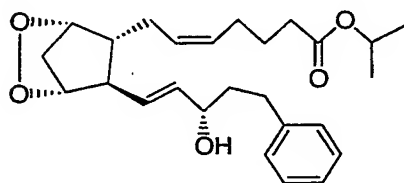
R₅ represents saturated or unsaturated acyclic hydrocarbons having from 1 to 20 carbon atoms, or --(CH₂)_qR₆, or a pharmaceutically acceptable salt of said compound.

36. A method in accordance with Claim 35 wherein the pro-drug is administered to decrease intraocular pressure in the eye of the mammal.

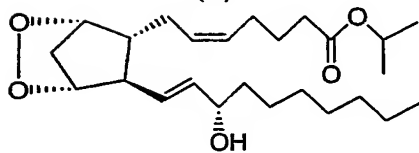
37. A method in accordance with Claim 36 wherein the compound is selected from the group consisting of compounds having the formulas (i) through (vii)



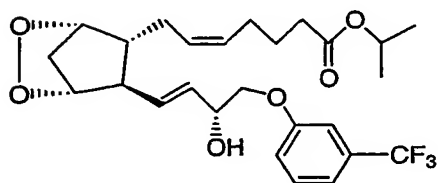
(i)



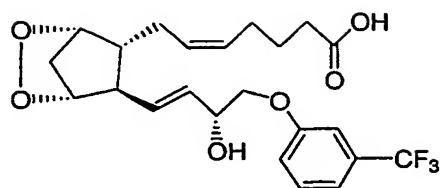
(ii)



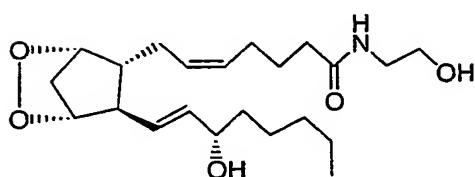
(iii)



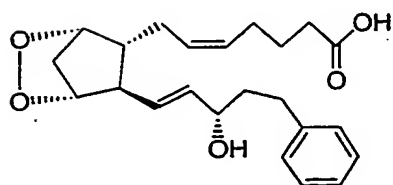
(iv)



(v)



(vi)



(vii)

38. A method in accordance with Claim 37 wherein the pro-drug is administered topically to decrease intraocular pressure in the eye of the mammal.

PATENT COOPERATION TREATY

International Application No. PCT/US 03/ 24305
International Filing Date: 04/ 08/ 2003
Applicant: ALLERGAN, INC.
Priority: 05/ 08/ 2002
Based on U.S. Serial No. 10/212,437
Attorney's Docket: 17497 (HL)

International Bureau of WIPO
34 chemin des Colombettes
1211 Geneva 20, Switzerland

STATEMENT UNDER ARTICLE 19(1) (Rule 46.4)

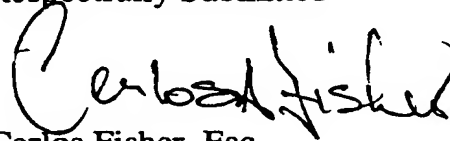
Claims were amended (as applicable) and Claim 24 was canceled to clearly and unequivocally avoid subject matter that came to applicant's attention during U.S. prosecution, namely the references *Bylund et al.* (J. Biol. Chem., 275 (29) pp 21844 – 21849) and/or the *Porter et al.* (J. Org. Chem. 48 (10) 1978 pp 2088 – 2090), and/or subject matter that applicant became aware of as a result of the International Search.

The foregoing was accomplished by adding provisos in Claims 1 and 13, and by deleting “=O” from the definition of the variable Y in Claim 1. Claim 11 was amended to correct an inadvertent error in the original claim language. The correction is supported by the specification where it is stated that “the variable X is preferably OH, OR₄ or NHR₄”.

Date: February 26, 2004

ALLERGAN, INC.
2525 Dupont Drive
Irvine, CA 92612

Respectfully Submitted


Carlos Fisher, Esq.